



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07K 5/023, A61K 38/06, 38/07		A1	(11) International Publication Number: WO 95/35308 (43) International Publication Date: 28 December 1995 (28.12.95)
<p>(21) International Application Number: PCT/US95/07617</p> <p>(22) International Filing Date: 16 June 1995 (16.06.95)</p> <p>(30) Priority Data: 08/261,452 17 June 1994 (17.06.94) US 08/405,581 17 March 1995 (17.03.95) US 08/440,898 25 May 1995 (25.05.95) US </p> <p>(71) Applicant: VERTEX PHARMACEUTICALS INCORPORATED [US/US]; 40 Allston Street, Cambridge, MA 02139-4211 (US).</p> <p>(72) Inventors: BEMIS, Guy, W.; 256 Appleton Street, Arlington, MA 02174 (US). GOLEC, Julian, M., C.; 8 Manor Farm, Chapel Road, Ashbury, Swindon, Wiltshire SN6 8LS (GB). LAUFPFER, David, J.; 254 Taylor Road, Stow, MA 01775 (US). MULLICAN, Michael, D.; 110 Parker Road, Needham, MA 02194 (US). MURCKO, Mark, A.; 520 Marshall Street, Holliston, MA 01746 (US). LIVINGSTON, David, J.; 20 Madison Avenue, Newtonville, MA 02160 (US).</p> <p>(74) Agents: HALEY, James, F., Jr. et al; Fish & Neave, 1251 Avenue of the Americas, New York, NY 10020-1104 (US).</p>		<p>(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, UZ, VN. European patent (AT, BE, CH, DE, DK, ES, FR, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> </p>	
<p>(54) Title: INHIBITORS OF INTERLEUKIN-1β CONVERTING ENZYME</p> <p>(57) Abstract</p> <p>The present invention relates to novel classes of compounds which are inhibitors of interleukin-1β converting enzyme. The ICE inhibitors of this invention are characterized by specific structural and physicochemical features. This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting ICE activity and consequently may be advantageously used as agents against interleukin-1 mediated diseases, including inflammatory diseases, autoimmune diseases and neurodegenerative diseases. This invention also relates to methods for inhibiting ICE activity and methods for treating interleukin-1 mediated diseases using the compounds and compositions of this invention.</p>			

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INHIBITORS OF INTERLEUKIN-1 β CONVERTING ENZYMETECHNICAL FIELD OF THE INVENTION

The present invention relates to novel
5 classes of compounds which are inhibitors of
interleukin-1 β converting enzyme ("ICE"). The ICE
inhibitors of this invention are characterized by
specific structural and physicochemical features. This
invention also relates to pharmaceutical compositions
10 comprising these compounds. The compounds and
pharmaceutical compositions of this invention are
particularly well suited for inhibiting ICE activity
and consequently, may be advantageously used as agents
against interleukin-1 ("IL-1") mediated diseases,
15 including inflammatory diseases, autoimmune diseases
and neurodegenerative diseases. This invention also
relates to methods for inhibiting ICE activity and
methods for treating interleukin-1 mediated diseases
using the compounds and compositions of this invention.

BACKGROUND OF THE INVENTION

Interleukin 1 ("IL-1") is a major pro-
inflammatory and immunoregulatory protein that
stimulates fibroblast differentiation and
proliferation, the production of prostaglandins,
25 collagenase and phospholipase by synovial cells and
chondrocytes, basophil and eosinophil degranulation and

- 2 -

neutrophil activation. Oppenheim, J.H. et al., Immunology Today, 7, pp. 45-56 (1986). As such, it is involved in the pathogenesis of chronic and acute inflammatory and autoimmune diseases. IL-1 is

5 predominantly produced by peripheral blood monocytes as part of the inflammatory response and exists in two distinct agonist forms, IL-1 α and IL-1 β . Mosely, B.S. et al., Proc. Natl. Acad. Sci., 84, pp. 4572-4576 (1987); Lonnemann, G. et al., Eur. J. Immunol., 19, 10 pp. 1531-1536 (1989).

IL-1 β is synthesized as a biologically inactive precursor, pIL-1 β . pIL-1 β lacks a conventional leader sequence and is not processed by a signal peptidase. March, C.J., Nature, 315, 15 pp. 641-647 (1985). Instead, pIL-1 β is cleaved by interleukin-1 β converting enzyme ("ICE") between Asp-116 and Ala-117 to produce the biologically active C-terminal fragment found in human serum and synovial fluid. Sleath, P.R., et al., J. Biol. Chem., 265, 20 pp. 14526-14528 (1992); A.D. Howard et al., J. Immunol., 147, pp. 2964-2969 (1991). Processing by ICE is also necessary for the transport of mature IL-1 β through the cell membrane.

ICE is a cysteine protease localized 25 primarily in monocytes. It converts precursor IL-1 β to the mature form. Black, R.A. et al., FEBS Lett., 247, pp. 386-390 (1989); Kostura, M.J. et al., Proc. Natl. Acad. Sci. USA, 86, pp. 5227-5231 (1989). ICE, or its homologues, also appears to be involved in the 30 regulation of cell death or apoptosis. Yuan, J. et al., Cell, 75, pp. 641-652 (1993); Miura, M. et al., Cell, 75, pp. 653-660 (1993); Nett-Fiordalisi, M.A. et al., J. Cell Biochem., 17B, p. 117 (1993). In particular, ICE or ICE homologues are thought to be 35 associated with the regulation of apoptosis in

- 3 -

neurodegenerative diseases, such as Alzheimer's and Parkinson's disease. Marx, J. and M. Baringa, Science, 259, pp. 760-762 (1993); Gagliardini, V. et al., Science, 263, pp. 826-828 (1994).

5 ICE has been previously described as a heterodimer composed of two subunits, p20 and p10 (20kDa and 10kDa molecular weight, respectively). These subunits are derived from a 45kDa proenzyme (p45) by way of a p30 form, through an activation mechanism
10 that is autocatalytic. Thornberry, N.A. et al., Nature, 356, pp. 768-774 (1992). The ICE proenzyme has been divided into several functional domains: a prodomain (p14), a p22/20 subunit, a polypeptide linker and a p10 subunit. Thornberry et al., supra; Casano
15 et al., Genomics, 20, pp. 474-481 (1994).

Full length p45 has been characterized by its cDNA and amino acid sequences. PCT patent applications WO 91/15577 and WO 94/00154. The p20 and p10 cDNA and amino acid sequences are also known. Thornberry et al., supra. Murine and rat ICE have also been sequenced and cloned. They have high amino acid and nucleic acid sequence homology to human ICE. Miller, D.K. et al., Ann. N.Y. Acad. Sci., 696, pp. 133-148 (1993); Molineaux, S.M. et al., Proc. Nat. Acad. Sci., 90, pp. 1809-1813 (1993). Knowledge of the primary structure of ICE, however, does not allow prediction of its tertiary structure. Nor does it afford an understanding of the structural, conformational and chemical interactions of ICE and its substrate pIL-1 β or other substrates or inhibitors.
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30 ICE inhibitors represent a class of compounds useful for the control of inflammation or apoptosis or both. Peptide and peptidyl inhibitors of ICE have been described. PCT patent applications WO 91/15577; WO 93/05071; WO 93/09135; WO 93/14777 and WO 93/16710; and
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- 4 -

European patent application 0 547 699. However, due to their peptidic nature, such inhibitors are typically characterized by undesirable pharmacologic properties, such as poor oral absorption, poor stability and rapid metabolism. Plattner, J.J. and D.W. Norbeck, in Drug Discovery Technologies, C.R. Clark and W.H. Moos, Eds. (Ellis Horwood, Chichester, England, 1990), pp. 92-126. This has hampered their development into effective drugs.

Accordingly, the need exists for compounds that can effectively inhibit the action of ICE, for use as agents for preventing and treating chronic and acute forms of IL-1 mediated diseases, including various cancers, as well as inflammatory, autoimmune or neurodegenerative diseases.

SUMMARY OF THE INVENTION

The present invention provides novel classes of compounds, and pharmaceutically acceptable derivatives thereof, that are useful as inhibitors of ICE. These compounds can be used alone or in combination with other therapeutic or prophylactic agents, such as antibiotics, immunomodulators or other anti-inflammatory agents, for the treatment or prophylaxis of diseases mediated by IL-1. According to a preferred embodiment, the compounds of this invention are capable of binding to the active site of ICE and inhibiting the activity of that enzyme.

It is a principal object of this invention to provide novel classes of inhibitors of ICE. These novel classes of ICE inhibitors are characterized by the following structural and physicochemical features:

- a) a first and a second hydrogen bonding moiety, each of said moieties being capable of forming a hydrogen bond with a different backbone atom

- 5 -

of ICE, said backbone atom being selected from the group consisting of the carbonyl oxygen of Arg-341, the amide -NH- group of Arg-341, the carbonyl oxygen of Ser-339 and the amide -NH- group of Ser-339;

5 b) a first and a second moderately hydrophobic moiety, said moieties each being capable of associating with a separate binding pocket of ICE when the inhibitor is bound thereto, said binding pocket being selected from the group consisting of the P2 binding pocket, the P3 binding pocket, the P4 binding pocket and the P' binding pocket; and

10 c) an electronegative moiety comprising one or more electronegative atoms, said atoms being attached to the same atom or to adjacent atoms in the moiety and said moiety being capable of forming one or more hydrogen bonds or salt bridges with residues in the P1 binding pocket of ICE.

15 It is also an object of this invention to provide a method for identification, design or prediction of ICE inhibitors comprising the steps of:

20 a) selecting a candidate compound of defined chemical structure comprising at least two hydrogen bonding moieties, at least two moderately hydrophobic moieties and one electronegative moiety comprising one or more electronegative atoms attached either to the same atom or to adjacent atoms in the electronegative moiety;

25 b) determining a low-energy conformation for binding of said compound to the active site of ICE;

c) evaluating the capability of said compound in said conformation to form at least two hydrogen bonds with the non-carbon backbone atoms of Arg-341 and Ser-339 of ICE;

30 d) evaluating the capability of said compound in said conformation to associate with at

- 6 -

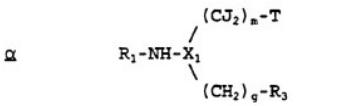
least two of the binding pockets of ICE selected from the group consisting of the P2 binding pocket, the P3 binding pocket, the P4 binding pocket and the P' binding pocket;

5 e) evaluating the capability of said compound in said conformation to interact with the P1 binding pocket of ICE; and

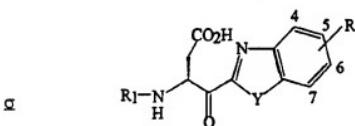
10 f) accepting or rejecting said candidate compound as an ICE inhibitor based on the determinations and evaluations carried out in the preceding steps.

It is a further object of this invention to provide novel classes of ICE inhibitors represented by formulas:

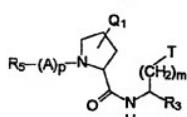
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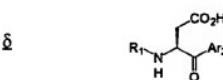
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- 7 -

ABBREVIATIONS AND DEFINITIONSAbbreviations

	<u>Designation</u>	<u>Reagent or Fragment</u>
	Ala	alanine
5	Arg	arginine
	Asn	asparagine
	Asp	aspartic acid
	Cys	cysteine
	Gln	glutamine
10	Glu	glutamic acid
	Gly	glycine
	His	histidine
	Ile	isoleucine
	Leu	leucine
15	Lys	lysine
	Met	methionine
	Phe	phenylalanine
	Pro	proline
	Ser	serine
20	Thr	threonine
	Trp	tryptophan
	Tyr	tyrosine
	Val	valine.

Definitions

25 The following terms are employed herein:

The term "active site" refers to any or all of the following sites in ICE: the substrate binding site, the site where an inhibitor binds and the site where the cleavage of substrate occurs. The active

30 site is characterized by at least amino acid residues: 173, 176, 177, 178, 179, 180, 236, 237, 238, 239, 244, 248, 283, 284, 285, 290, 338, 339, 340, 341, 342, 343,

- 8 -

344, 345, 348, 352, 381, 383, using the sequence and
numbering according to Thornberry et al., supra.

The terms "P binding pocket", "S subsite", "S
5 pocket", and the like, refer to binding subsites, or
portions of the substrate binding site on the ICE
molecule. The amino acid residues of the substrate are
given designations according to their position relative
to the scissile bond, i.e. the bond which is broken by
the protease. The residues are designated P₁, P₂,
10 etc., for those extending toward the N-terminus of the
substrate and P_{1'}, P_{2'}, etc., for those extending
toward the C-terminus of the substrate. The portions
of an inhibitor which correspond to the P or P'
residues of the substrate are also labeled P₁, P_{1'},
15 etc., by analogy with the substrate. The binding
subsites of the ICE molecule which receive the residues
labeled P₁, P_{1'}, etc., are designated S₁, S_{1'}, etc., or
may alternately be designated "the P₁ binding pocket",
"the P_{1'} binding pocket", etc. [I. Schechter and A.
20 Berger, "On the Size of the Active Site in Proteases",
Biochem. Biophys. Res. Commun., vol. 27, pp. 157-162
(1967).]

The terms "P₂ binding pocket" or "S₂ subsite"
25 of the ICE active site are equivalent and are defined
as the space surrounded by amino acid residues Pro-290,
Val-338 or Trp-340.

The terms "P₃ binding pocket" or "S₃ subsite"
30 of the ICE active site are equivalent and are defined
as the space surrounded by amino acid residues Pro-177,
Arg-178, Thr-180, Arg-341 or Pro-343.

The terms "P₄ binding pocket" or "S₄ subsite"
35 of the ICE active site are equivalent and are defined
as the space surrounded by amino acid residues His-342,
Met-345, Val-348, Arg-352, Asp-381, Arg-383 or Trp-340.

- 9 -

The terms "P1 binding pocket" or "S1 subsite" of the ICE active site are equivalent and are defined as the space surrounded by amino acid residues Arg-179, His-237, Gln-283, or Arg-341.

5 The terms "P' binding pocket" or "S' subsite" of the ICE active site are equivalent and are defined as the space surrounded by amino acid residues Phe-173, Ile-176, His-237, Gly-238, Ile-239, Cys-244 or His-248.

10 The term "hydrophobic" refers to a moiety which tends not to dissolve in water and is fat-soluble. Hydrophobic moieties include, but are not limited to, hydrocarbons, such as alkanes, alkenes, alkynes, cycloalkanes, cycloalkenes, cycloalkynes and aromatic compounds, such as aryls, certain saturated 15 and unsaturated heterocycles and moieties that are substantially similar to the side chains of hydrophobic natural and unnatural α -amino acids, including valine, leucine, isoleucine, methionine, phenylalanine, α -amino isobutyric acid, alloisoleucine, tyrosine, and 20 tryptophan.

25 The term "moderately hydrophobic" refers to a hydrophobic moiety in which one or two carbon atoms have been replaced with more polar atoms, such as oxygen or nitrogen.

30 The term "heterocycle" or "heterocyclic" refers to a stable mono- or polycyclic compound which may optionally contain one or two double bonds or may optionally contain one or more aromatic rings. Each heterocycle consists of carbon atoms and from one to four heteroatoms independently selected from a group including nitrogen, oxygen, and sulfur. As used herein, the terms "nitrogen heteroatoms" and "sulphur heteroatoms" include any oxidized form of nitrogen or sulfur and the quaternized form of any basic nitrogen. 35 Heterocycles defined above include, for example,

- 10 -

pyrimidinyl, tetrahydroquinolyl,
tetrahydroisoquinonlanyl, purinyl, pyrimidyl,
indolinyl, benzimidazolyl, imidazolyl, imidazolinoyl,
imidazolidinyl, quinolyl, isoquinolyl, indolyl,
5 pyridyl, pyrrolyl, pyrrolinyl, pyrazolyl, pyrazinyl,
quinoxolyl, piperidinyl, morpholinyl, thiamorpholinyl,
furyl, thieryl, triazolyl, thiazolyl, β -carbolinyl,
tetrazolyl, thiazolidinyl, benzofuranoyl,
thiamorpholinyl sulfone, benzoxazolyl, oxopiperidinyl,
10 oxopyrroldinyl, oxoazepinyl, azepinyl, isoxazolyl,
tetrahydropyranyl, tetrahydrofuranyl, thiadiazolyl,
benzodioxolyl, benzothienyl, tetrahydrothiophenyl and
sulfolanyl. Further heterocycles are described in A.R.
Katritzky and C.W. Rees, eds., Comprehensive
15 Heterocyclic Chemistry: The Structure, Reactions,
Synthesis and Use of Heterocyclic Compounds, Vol. 1-8,
Pergamon Press, NY (1984).

The term "cycloalkyl" refers to a mono- or
polycyclic group which contains 3 to 15 carbons and may
20 optionally contain one or two double bonds. Examples
include cyclohexyl, adamantyl and norbornyl.

The term "aryl" refers to a mono- or
polycyclic group which contains 6, 10, 12, or 14
carbons in which at least one ring is aromatic.
25 Examples include phenyl, naphthyl and biphenyl.

The term "heteroaromatic" refers to a mono-
or polycyclic group which contains 1 to 15 carbon atoms
and from 1 to 4 heteroatoms, each of which is selected
independently from a group including sulphur, nitrogen
30 and oxygen, and which additionally contains from 1 to 3
five or six membered rings, at least one of which is
aromatic.

The term "alpha-amino acid" (α -amino acid)
refers to both the naturally occurring amino acids and
35 other "non-protein" α -amino acids commonly utilized by

- 11 -

those in the peptide chemistry arts when preparing synthetic analogues of naturally occurring peptides, including D and L forms. The naturally occurring amino acids are glycine, alanine, valine, leucine, iso-leucine, serine, methionine, threonine, phenylalanine, tyrosine, tryptophan, cysteine, proline, histidine, aspartic acid, asparagine, glutamic acid, glutamine, γ -carboxyglutamic acid, arginine, ornithine and lysine.

Examples of "non-protein" alpha-amino acids include

hydroxylysine, homoserine, homotyrosine, homo-phenylalanine, citrulline, kynurenine, 4-amino-phenylalanine, 3-(2-naphthyl)-alanine, 3-(1-naphthyl)-alanine, methionine sulfone, t-butyl-alanine, t-butylglycine, 4-hydroxyphenylglycine, aminoalanine, phenylglycine, vinylalanine, propargyl-glycine, 1,2,4-triazolo-3-alanine, 4,4,4-trifluoro-threonine, thyronine, 6-hydroxytryptophan, 5-hydro-xytryptophan, 3-hydroxypyridine, 3-aminotyrosine, trifluoromethyl-alanine, 2-thienylalanine, (2-(4-pyridyl)ethyl)-cysteine, 3,4-dimethoxy-phenylalanine, 3-(2-thiazolyl)-alanine, ibotenic acid, 1-amino-1-cyclopentane-carboxylic acid, 1-amino-1-cyclohexanecarboxylic acid, quisqualic acid, 3-trifluoromethylphenylalanine, 4-trifluoro-methylphenylalanine, cyclohexylalanine, cyclo-hexylglycine, thiohistidine, 3-methoxytyrosine, elastatinal, norleucine, norvaline, alioisoleucine, homarginine, thioproline, dehydroproline, hydroxy-proline, isonipectotic acid, homoproline, cyclohexyl-glycine, α -amino-n-butyric acid, cyclohexylalanine, aminophenylbutyric acid, phenylalanines substituted at the ortho, meta, or para position of the phenyl moiety with one or two of the following: a (C₁-C₄) alkyl, a (C₁-C₄) alkoxy, halogen or nitro groups or substituted with a methylenedioxy group; S-2- and 3-thienyl-alanine, S-2- and 3-furanylalanine, S-2-, 3- and

- 12 -

4-pyridylalanine, β -(benzothienyl-2- and 3-yl)alanine,
5 β -(1- and 2-naphthyl)alanine, O-alkylated derivatives
of serine, threonine or tyrosine, S-alkylated cysteine,
S-alkylated homocysteine, O-sulfate, O-phosphate and O-
carboxylate esters of tyrosine, 3-sulfo-tyrosine, 3-
10 carboxy-tyrosine, 3-phospho-tyrosine, 4-methane
sulfonic acid ester of tyrosine, 4-methane phosphonic
acid ester of tyrosine, 3,5-diiodotyrosine, 3-nitro-
tyrosine, ϵ -alkyl lysine, and delta-alkyl ornithine.
15 Any of these α -amino acids may be substituted with a
methyl group at the alpha position, a halogen at any
aromatic residue on the α -amino side chain, or an
appropriate protective group at the O, N, or S atoms of
the side chain residues. Appropriate protective groups
20 are disclosed in "Protective Groups In Organic
Synthesis," T.W. Greene and P.G.M. Wuts, J. Wiley &
Sons, NY, NY, 1991.

The term " α -amino acid side chain residue"
25 refers to a chemical moiety which is attached to the α -
carbon of an alpha-amino acid.

The term "bioisosteric replacement for $-\text{CO}_2\text{H}$ "
refers to group which may substitute for a carboxylic
acid group in bioactive molecules. Examples of such
groups are disclosed in Christopher A. Lipinski,
25 "Bioisosteres in Drug Design" Annual Reports In Medical
Chemistry, 21, pp. 286-88 (1986), and in C.W. Thornber,
"Isosterism and Molecular Modification in Drug Design"
Chemical Society Reviews, pp. 563-580 (1979).

The term "association" is used in reference
30 to a condition of proximity between an inhibitor or
portions thereof to an ICE molecule or portions thereof
wherein the juxtaposition is energetically favored by
electrostatic or van der Waals interactions.

The term "hydrogen bond" refers to a
35 favorable interaction that occurs whenever a suitable

- 13 -

donor atom, X, bearing a proton, H, and a suitable acceptor atom, Y, have a separation of between 2.5Å and 3.5Å and where the angle X-H - - - Y is greater than 90 degrees. Suitable donor and acceptor atoms are well understood in medicinal chemistry (G.C. Pimentel and A.L. McClellan, The Hydrogen Bond, Freeman, San Francisco, 1960; R. Taylor and O. Kennard, "Hydrogen Bond Geometry in Organic Crystals", Accounts of Chemical Research, 17, pp. 320-326 (1984)).

The term "salt bridge" refers to the non-covalent attractive interaction between a positively charged moiety (P) and a negatively charged moiety (N) when the distance between the centers of mass of P and N is between 2 and 6 Angstroms. In calculating the center of mass, atoms which may contain a formal charge and atoms immediately adjacent to these are included. For example, a salt bridge may be formed between the positively charged guanidinium side chain of an arginine residue and the negative charged carboxylate side chain of a glutamate residue. Salt bridges are well understood in medicinal chemistry (L. Stryer, Biochemistry, Freeman, San Francisco, (1975); K.A. Dill, "Dominant Forces in Protein Folding", Biochemistry, 29, No. 31, pp. 7133-7155, (1990)).

The term "center of mass" refers to a point in three-dimensional space which represents a weighted average position of the masses that make up an object.

The terms "backbone chain" and "backbone" refer to the portion of a polypeptide which comprises the repeating unit -CO-CH-NH-.

The term "scaffold" refers to a structural building block which forms the basis of an ICE inhibitor according to this invention. Various moieties and functional groups are intended to be appended to the scaffold. The scaffolds of this

- 14 -

invention are thus depicted having open valences.
 Various scaffolds of ICE inhibitors according to this
 invention include the portions:



or



- 15 In those scaffolds, the NH and CO or SO₂ moieties represent a first and a second hydrogen bonding moiety, said moieties each being capable of forming a hydrogen bond with a backbone atom of ICE, said backbone atom being selected from the group consisting of the
 20 carbonyl oxygen of Arg-341, the amide -NH- of Arg-341, the carbonyl oxygen of Ser-339 and the amide -NH- of Ser-339.

The term "substitute" refers to the replacement of a hydrogen atom in a compound with a substituent group. In the present invention, those hydrogen atoms which form a part of a hydrogen bonding moiety which is capable of forming a hydrogen bond with the carbonyl oxygen of Arg-341 of ICE or the carbonyl oxygen of Ser-339 of ICE are excluded from substitution. These excluded hydrogen atoms include those which comprise an -NH- group which is alpha to a Z or a -CO- group and are depicted as -NH- rather than an X group or some other designation in the following diagrams: (a) through (t), (v) through (y), and (I) through (VIID).

- 15 -

The term "straight chain" refers to a contiguous unbranching string of covalently bound members, i.e. atoms, which form a portion of a ring. The straight chain and the ring of which it forms a part may be substituted, but these substituents are not a part of the straight chain.

5 The term " K_i " refers to a numerical measure of the effectiveness of a compound in inhibiting the activity of a target enzyme such as ICE. Lower values 10 of K_i reflect higher effectiveness. The K_i value is a derived by fitting experimentally determined rate data to standard enzyme kinetic equations (see I. H. Segel, Enzyme Kinetics, Wiley-Interscience, 1975).

15 The term "minimize" refers to the systematic altering of the atomic geometry of a molecule or molecular complex so that any further minor perturbation of the atomic geometry would cause the total energy of the system as measured by a molecular mechanics force-field to increase. Minimization and 20 molecular mechanics force-fields are well understood in computational chemistry [U. Burkert and N.L. Allinger, Molecular Mechanics, ACS Monograph 177, American Chemical Society, Washington, D.C. 1982 pages 59-78].

25 The term "strain energy" is used in this application to refer to the difference between the free conformation energy of a compound and the bound conformation energy of that compound when bound to ICE. The strain energy can be determined by the following steps: Evaluate the energy of the molecule when it has 30 the conformation necessary for binding to ICE. Then minimize and reevaluate the energy -- this is the free conformation energy. The strain energy for binding of a potential inhibitor to ICE is the difference between the free conformation energy and the bound conformation 35 energy. In a preferred embodiment, the strain energy

- 16 -

of an inhibitor of the present invention is less than about 10 kcal/mol.

The term "patient" as used in this application refers to any mammal, especially humans.

5 The term "pharmaceutically effective amount" refers to an amount effective in treating or ameliorating an IL-1 mediated disease in a patient. The term "prophylactically effective amount" refers to an amount effective in preventing or substantially 10 lessening IL-1 mediated disease in a patient.

The term "pharmaceutically acceptable carrier or adjuvant" refers to a non-toxic carrier or adjuvant that may be administered to a patient, together with a compound of this invention, and which does not destroy 15 the pharmacological activity thereof.

15 The term "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, ester, or salt of such ester, of a compound of this invention or any other compound which, upon 20 administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention or an anti-ICE active metabolite or residue thereof.

Pharmaceutically acceptable salts of the 25 compounds of this invention include, for example, those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfonic, 30 tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, 35 may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the

- 17 -

invention and their pharmaceutically acceptable acid addition salts. Salts derived from appropriate bases include alkali metal (e.g., sodium), alkaline earth metal (e.g., magnesium), ammonium and N-(C₁₋₄ alkyl)₄⁺ salts.

This invention also envisions the "quaternization" of any basic nitrogen-containing groups of the compounds disclosed herein. The basic nitrogen can be quaternized with any agents known to those of ordinary skill in the art including, for example, lower alkyl halides, such as methyl, ethyl, propyl and butyl chloride, bromides and iodides; dialkyl sulfates including dimethyl, diethyl, dibutyl and diethyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; and aralkyl halides including benzyl and phenethyl bromides. Water or oil-soluble or dispersible products may be obtained by such quaternization.

The ICE inhibitors of this invention may contain one or more "asymmetric" carbon atoms and thus may occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be of the R or S configuration. Although specific compounds and scaffolds exemplified in this application may be depicted in a particular stereochemical configuration, compounds and scaffolds having either the opposite stereochemistry at any given chiral center or mixtures thereof are also envisioned.

The ICE inhibitors of this invention may comprise ring structures which may optionally be substituted at carbon, nitrogen or other atoms by

- 18 -

various substituents. Such ring structures may be singly or multiply substituted. Preferably, the ring structures contain between 0 and 3 substituents. When multiply substituted, each substituent may be picked 5 independently of any other substituent as long as the combination of substituents results in the formation of a stable compound.

Combinations of substituents and variables envisioned by this invention are only those that result 10 in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and administration to a mammal by methods known in the art. Typically, such compounds are stable at a temperature 15 of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

DETAILED DESCRIPTION OF THE INVENTION

In order that the invention herein described 20 may be more fully understood, the following detailed description is set forth.

We have discovered that compounds possessing the following novel combination of features are surprisingly effective ICE inhibitors:

a) a first and a second hydrogen bonding 25 moiety, each of said moieties being capable of forming a hydrogen bond with a different backbone atom of ICE, said backbone atom being selected from the group consisting of the carbonyl oxygen of Arg-341, the amide -NH- group of Arg-341, the carbonyl oxygen of Ser-339 and the amide -NH- group of Ser-339;

b) a first and a second moderately 30 hydrophobic moiety, said moieties each being capable of associating with a separate binding pocket of ICE when the inhibitor is bound thereto, said binding pocket

- 19 -

being selected from the group consisting of the P2 binding pocket, the P3 binding pocket, the P4 binding pocket and the P' binding pocket; and

5 c) an electronegative moiety comprising one or more electronegative atoms, said atoms being attached to the same atom or to adjacent atoms in the moiety and said moiety being capable of forming one or more hydrogen bonds or salt bridges with residues in the P1 binding pocket of ICE.

10 Preferably, any moderately hydrophobic moiety associating with the P2 binding pocket of ICE does so in such a way that:

15 a) the distance from the center of mass of the moderately hydrophobic moiety in the P2 binding pocket to the carbonyl oxygen of Arg-341 of ICE is between about 7.1Å and about 12.5Å;

20 b) the distance from the center of mass of the moderately hydrophobic moiety in the P2 binding pocket to the amide nitrogen of Arg-341 of ICE is between about 6.0Å and about 12Å; and

c) the distance from the center of mass of the moderately hydrophobic moiety in the P2 binding pocket to the carbonyl oxygen of Ser-339 of ICE is between about 3.7Å and about 9.5Å.

25 Preferably, any moderately hydrophobic moiety associating with the P3 binding pocket of ICE does so in such a way that:

30 a) the distance from the center of mass of the moderately hydrophobic moiety in the P3 binding pocket to the carbonyl oxygen of Arg-341 of ICE is between about 3.9Å and about 9.5Å;

b) the distance from the center of mass of the moderately hydrophobic moiety in the P3 binding pocket to the amide nitrogen of Arg-341 of ICE is between about 5.4Å and about 11Å; and

- 20 -

c) the distance from the center of mass of the moderately hydrophobic moiety in the P3 binding pocket to the carbonyl oxygen of Ser-339 of ICE is between about 7.0Å and about 13Å.

5 Preferably, any moderately hydrophobic moiety associating with the P4 binding pocket of ICE does so in such a way that:

a) the distance from the center of mass of the moderately hydrophobic moiety in the P4 binding pocket to the carbonyl oxygen of Arg-341 of ICE is between about 4.5Å and about 7.5Å;

b) the distance from the center of mass of the moderately hydrophobic moiety in the P4 binding pocket to the amide nitrogen of Arg-341 of ICE 15 is between about 5.5Å and about 8.5Å; and

c) the distance from the center of mass of the moderately hydrophobic moiety in the P4 binding pocket to the carbonyl oxygen of Ser-339 of ICE is between about 8Å and about 11Å.

20 Preferably, any moderately hydrophobic moiety associating with the P' binding pocket of ICE does so in such a way that:

a) the distance from the center of mass of the moderately hydrophobic moiety in the P' binding pocket to the carbonyl oxygen of Arg-341 of ICE 25 is between about 11Å and about 16Å;

b) the distance from the center of mass of the moderately hydrophobic moiety in the P' binding pocket to the amide nitrogen of Arg-341 of ICE 30 is between about 10Å and about 15Å; and

c) the distance from the center of mass of the moderately hydrophobic moiety in the P' binding pocket to the carbonyl oxygen of Ser-339 of ICE is between about 8Å and about 12Å.

- 21 -

More preferably, all of the above associative conditions are met in the compounds of this invention.

The practitioner skilled in the art will appreciate that there are a number of means to design the inhibitors of the present invention. These same means may be used to select a candidate compound for screening as an ICE inhibitor. This design or selection may begin with selection of the various moieties which fill binding pockets.

There are a number of ways to select moieties to fill individual binding pockets. These include visual inspection of a physical model or computer model of the active site and manual docking of models of selected moieties into various binding pockets.

Modeling software that is well known and available in the art may be used. These include QUANTA [Molecular Simulations, Inc., Burlington, MA, 1992], SYBYL [Molecular Modeling Software, Tripos Associates, Inc., St. Louis, MO, 1992], AMBER [S.J. Weiner, P.A. Kollman, D.A. Case, U.C. Singh, C. Ghio, G. Alagona, and P. Weiner, J. Am. Chem. Soc., vol. 106, pp. 765-784 (1984)], or CHARMM [B.R. Brooks, R.E. Bruckolieri, B.D. Olafson, D.J. States, S Swaminathan, and M. Karplus, J. Comp. Chem. vol. 4, pp. 187-217 (1983)]. This

modelling step may be followed by energy minimization with standard molecular mechanics forcefields such as CHARMM and AMBER. In addition, there are a number of more specialized computer programs to assist in the process of selecting the binding moieties of this invention. These include:

1. GRID (Goodford, P.J. A Computational Procedure for Determining Energetically Favorable Binding Sites on Biologically Important Macromolecules. J. Med. Chem., 28, pp. 849-857 (1985)). GRID is available from Oxford University, Oxford, UK.

- 22 -

2. MCSS (Miranker, A.; Karplus, M. Functionality Maps of Binding Sites: A Multiple Copy Simultaneous Search Method. Proteins: Structure, Function and Genetics, 11, pp. 29-34 (1991)). MCSS is available from Molecular Simulations, Burlington, MA.
- 5
3. AUTODOCK (Goodsell, D.S.; Olsen, A.J. Automated Docking of Substrates to Proteins by Simulated Annealing. PROTEINS: Structure, Function and Genetics, 8, pp. 195-202 (1990)). AUTODOCK is available from the Scripps Research Institute, La Jolla, CA.
- 10
4. DOCK (Kuntz, I.D.; Blaney, J.M.; Oatley, S.J.; Langridge, R.; Ferrin, T.E. A Geometric Approach to Macromolecule-Ligand Interactions. J. Mol. Biol., 161, pp. 269-288 (1982)). DOCK is available from the University of California, San Francisco, CA.
- 15

Once suitable binding moieties have been selected, they can be assembled into a single inhibitor. This assembly may be accomplished by connecting the various moieties to a central scaffold. The assembly process may, for example, be done by visual inspection followed by manual model building, again using software such as Quanta or Sybyl. A number of other programs may also be used to help select ways to connect the various moieties. These include:

20

1. CAVEAT (Bartlett, P.A.; Shea, G.T.; Telfer, S.J.; Waterman, S. CAVEAT: A Program to Facilitate the Structure-Derived Design of Biologically Active Molecules. In "Molecular Recognition in Chemical and Biological Problems," Special Pub., Royal Chem. Soc., 78, pp. 182-196 (1989)). CAVEAT is available from the University of California, Berkeley, CA.

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2. 3D Database systems such as MACCS-3D (MDL Information Systems, San Leandro, CA). This area has been recently reviewed by Martin (Martin, Y.C. 3D Database Searching in Drug Design. J. Med. Chem., 35, pp. 2145-2154 (1992)).

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- 23 -

3. HOOK (available from Molecular Simulations, Burlington, MA).

5 In addition to the above computer assisted modeling of inhibitor compounds, the inhibitors of this invention may be constructed "de novo" using either an empty active site or optionally including some portions of a known inhibitor. Such methods are well known in the art. They include, for example:

10 1. LUDI (Bohm, H.J. The Computer Program LUDI: A New Method for the De Novo Design of Enzyme Inhibitors. J. Comp. Aid. Molec. Design., 6, 61-78 (1992)). LUDI is available from Biosym Technologies, San Diego, CA.

15 2. LEGEND (Nishibata, Y., Itai, A., Tetrahedron, 47, 8985 (1991)). LEGEND is available from Molecular Simultations, Burlington, MA.

20 3. LeapFrog (available from Tripos associates, St. Louis, MO).

A number of techniques commonly used for modeling drugs may be employed (For a review, see: Cohen, N.C.; Blaney, J.M.; Humblet, C.; Gund, P.; Barry, D.C., "Molecular Modeling Software and Methods for Medicinal Chemistry", J. Med. Chem., 33, pp. 883-894 (1990)). There are likewise a number of examples in the chemical literature of techniques that can be applied to specific drug design projects. For a review, see: Navia, M.A. and Murcko, M.A., "The Use of Structural Information in Drug Design", Current Opinions in Structural Biology, 2, pp. 202-210 (1992). Some examples of these specific applications include: Baldwin, J.J. et al., "Thienothiopyran-2-sulfonamides: Novel Topically Active Carbonic Anhydrase Inhibitors for the Treatment of Glaucoma", J. Med. Chem., 32, pp. 2510-2513 (1989); Appelt, K. et al., "Design of Enzyme Inhibitors Using Iterative Protein Crystallographic Analysis", J. Med. Chem., 34, pp. 1925-1934 (1991); and

- 24 -

Ealick, S.E. et al., "Application of Crystallographic and Modeling Methods in the Design of Purine Nucleotide Phosphorylase Inhibitors" Proc. Nat. Acad. Sci. USA, 88, pp. 11540-11544 (1991).

5 Using the novel combination of steps of the present invention, the skilled artisan can advantageously avoid time consuming and expensive experimentation to determine enzymatic inhibition activity of particular compounds. The method also is
10 useful to facilitate rational design of ICE inhibitors and therapeutic and prophylactic agents against IL-1-mediated diseases. Accordingly, the present invention relates to such inhibitors.

15 A variety of conventional techniques may be used to carry out each of the above evaluations as well as the evaluations necessary in screening a candidate compound for ICE inhibiting activity. Generally, these techniques involve determining the location and binding proximity of a given moiety, the occupied space of a bound inhibitor, the deformation energy of binding of a given compound and electrostatic interaction energies. Examples of conventional techniques useful in the above evaluations include: quantum mechanics, molecular mechanics, molecular dynamics, Monte Carlo sampling, systematic searches and distance geometry methods (G.R. Marshall, Ann. Ref. Pharmacol. Toxicol., 27, p. 193 (1987)). Specific computer software has been developed for use in carrying out these methods. Examples of programs designed for such uses include: Gaussian 92, revision E.2 (M.J. Frisch, Gaussian, Inc., Pittsburgh, PA ©1993); AMBER, version 4.0 (P.A. Kollman, University of California at San Francisco, ©1993); QUANTA/CHARMM [Molecular Simulations, Inc., Burlington, MA ©1992]; and Insight II/Discover (Biosym Technologies Inc., San Diego, CA ©1992). These programs may be implemented,
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- 25 -

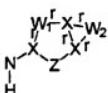
for instance, using a Silicon Graphics Indigo 2 workstation or IBM RISC/6000 workstation model 550. Other hardware systems and software packages will be known and of evident applicability to those skilled in the art.

Different classes of active ICE inhibitors, according to this invention, may interact in similar ways with the various binding pockets of the ICE active site. The spatial arrangement of these important groups is often referred to as a pharmacophore. The concept of the pharmacophore has been well described in the literature (D. Mayer, C.B. Naylor, I. Motoc, and G.R. Marshall, J. Comp. Aided Molec. Design vol. 1, pp. 3-16 (1987); A. Hopfinger and B.J. Burke, in Concepts and Applications of Molecular Similarity, M.A. Johnson and G.M. Maggiora, ed., Wiley (1990)).

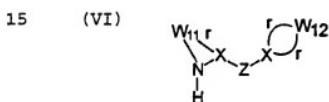
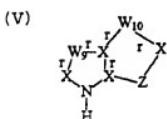
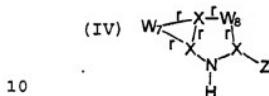
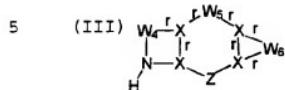
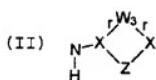
Different classes of ICE inhibitors of this invention may also use different scaffolds or core structures, but all of these cores will allow the necessary moieties to be placed in the active site such that the specific interactions necessary for binding may be obtained. These compounds are best defined in terms of their ability to match the pharmacophore, i.e., their structural identity relative to the shape and properties of the active site of ICE.

The ICE inhibitors of one embodiment of this invention comprise a first and a second hydrogen bonding moiety, a first and a second moderately hydrophobic moiety, and an electronegative moiety which comprise or are covalently bound to one of the following scaffolds:

(I)



- 26 -



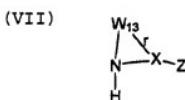
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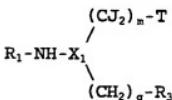
; and



20

The ICE inhibitors of another embodiment (A) of this invention are those of formula α :

25

 α 

- 27 -

wherein:

X₁ is CH or N;

g is 0 or 1;

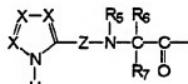
each J is independently selected from the group
 5 consisting of -H, -OH, and -F, provided that when a
 first and second J are bound to a C and said first J is
 -OH, said second J is -H;

m is 0, 1, or 2;

T is -Ar₃, -OH, -CF₃, -CO-CO₂H, -CO₂H or any
 10 bioisosteric replacement for -CO₂H;

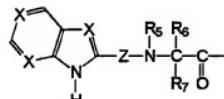
R₁ is selected from the group consisting of the
 following formulae, in which any ring may optionally be
 singly or multiply substituted at any carbon by Q₁, at
 any nitrogen by R₅, or at any atom by =O, -OH, -CO₂H, or
 15 halogen, and in which any saturated ring may optionally
 be unsaturated at one or two bonds:

(a)



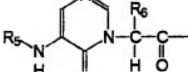
;

(b)



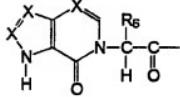
;

(c)



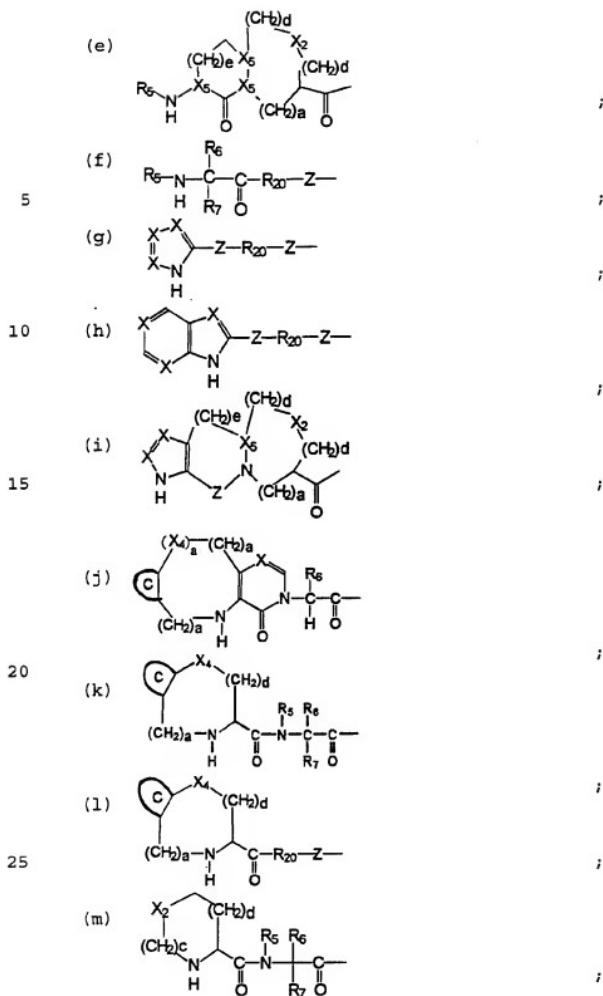
;

(d)

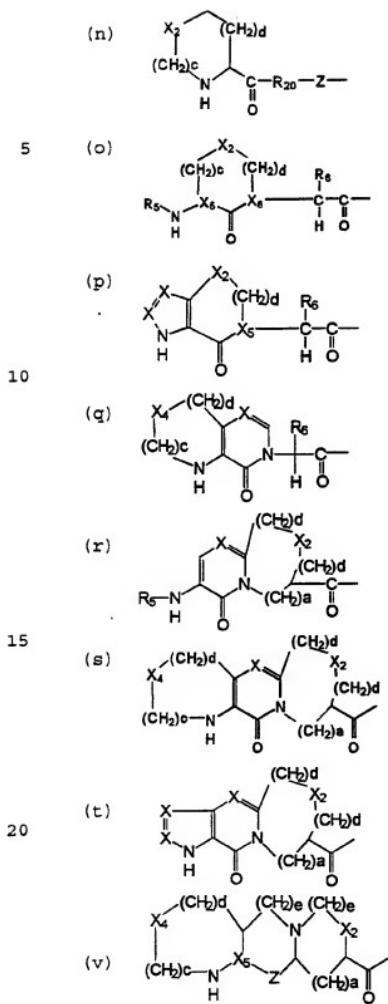


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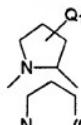
- 29 -



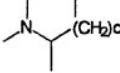
- 30 -

R₂₀ is selected from the group consisting of:

(aa1)



(aa2)



5

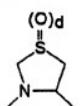
(aa3)



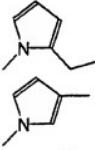
(aa4)



10 (aa5)



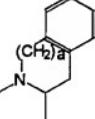
15 (bb)



(cc)



(dd)

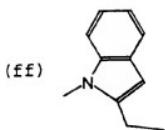


(ee)



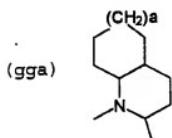
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- 31 -



(gg)

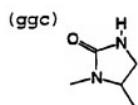
5



(gggb)

10

i and



15

wherein each ring C is independently chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

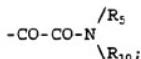
R₂ is

20

- CN,
- CH=CH-R₉,
- CH=N-O-R₉,
- (CH₂)₁₋₃-T,
- CJ₂-R₉,
- CO-R₁₃, O-

25

- 32 -



each R_4 is independently selected from the group
5 consisting of:

- H,
- Ar₁,
- R₉,
- T₁-R₉, and
- 10 - (CH₂)_{1,2,3}-T₁-R₉,

each T₁ is independently selected from the group
consisting of:

- CH=CH-,
- O-,
- 15 -S-,
- SO-,
- SO₂-,
- NR₁₀-,
- NR₁₀-CO-,
- 20 -CO-,
- O-CO-,
- CO-O-,
- CO-NR₁₀-,
- O-CO-NR₁₀-,
- 25 -NR₁₀-CO-O-,
- NR₁₀-CO-NR₁₀-,
- SO₂-NR₁₀-,
- NR₁₀-SO₂-, and
- NR₁₀-SO₂-NR₁₀-,

30 each R₅ is independently selected from the group
consisting of:

- H,
- Ar₁,

-CO-Ar₁,
 -SO₂-Ar₁,
 -R₉,
 -CO-R₉,
 5 -CO-O-R₉,
 -SO₂-R₉,
 /Ar₁
 -CO-N
 \R₁₀,
 10 /Ar₁
 -SO₂-N
 \R₁₀,
 /R₉
 -CO-N
 \R₁₀, and
 /R₉
 -SO₂-N
 \R₁₀,

R₆ and R₇ taken together form a saturated 4-8
 20 member carbocyclic ring or heterocyclic ring containing
 -O-, -S-, or -NH-, or
 R₇ is -H and R₆ is
 -H
 -Ar₁,
 25 -R₉, or
 -(CH₂)_{1,2,3}-T₁-R₉;

each R₉ is a C₁₋₆ straight or branched alkyl group
 optionally singly or multiply substituted by -OH, -F,
 or =O and optionally substituted with one or two Ar₁
 30 groups;

each R₁₀ is independently selected from the group
 consisting of -H or a C₁₋₆ straight or branched alkyl
 group;

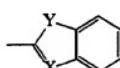
- 34 -

each R₁ is independently selected from the group consisting of -Ar₂ and -R₄;

each Ar₁ is a cyclic group independently selected from the set consisting of an aryl group which contains 5 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 15 carbon atoms and between 1 and 3 rings, said cycloalkyl group being optionally benzofused, and a heterocycle group containing between 5 and 15 ring 10 atoms and between 1 and 3 rings, said heterocycle group containing at least one heteroatom group selected from -O-, -S-, -SO-, -SO₂-, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or 15 more aromatic rings, and said cyclic group optionally being singly or multiply substituted by =O, -OH, perfluoro C₁-, alkyl, or -Q₁;

each Ar₂ is independently selected from the 20 following group, in which any ring may optionally be substituted by -Q₁:

(hh)



;

(ii)



;

(jj)



; and

(kk)



;

30

- 35 -

Ar₁ is a cyclic group selected from the set consisting of a phenyl ring, a 5-membered heteroaromatic ring, and a 6-membered heteroaromatic ring, said heteroaromatic rings comprising 1-3 heteroatom groups selected from -O-, -S-, -SO-, -SO₂-, =N-, and -NH-, said cyclic group optionally being singly or multiply substituted with =O, -OH, halogen, perfluoro C₁₋₃ alkyl, or -CO₂H;

each Q₁ is independently selected from the group consisting of:

-Ar₁,
-R₉,
-T₁-R₉, and
-(CH₂)_{1,2,3}-T₁-R₉,

provided that when -Ar₁ is substituted with a Q₁ group which comprises one or more additional -Ar₁ groups, said additional -Ar₁ groups are not substituted with Q₁;

each X is independently selected from the group consisting of =N-, and =CH-;

each X₂ is independently selected from the group consisting of -O-, -CH₂-, -NH-, -S-, -SO-, and -SO₂;
each X₃ is independently selected from the group consisting of -CH₂-, -S-, -SO-, and -SO₂;

each X₄ is independently selected from the group consisting of -CH₂- and -NH-;

each X₅ is independently selected from the group consisting of -CH- and -N-;

- 36 -

X_6 is CH or N, provided that when X_6 is N in the R₁ group labeled (o) and X_5 is CH and X_2 is CH_2 the ring of the R₁ group labeled (o) must be substituted by Q₁ or benzofused;

each Y is independently selected from the group consisting of -O- and -S-;

each Z is independently CO or SO₂,

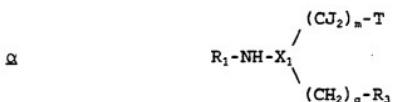
each a is independently 0 or 1,

each c is independently 1 or 2.

each d is independently 0, 1, or 2, and

each e is independently 0, 1, 2, or 3.

The ICE inhibitors of another embodiment (B) of this invention are those of formula α :



20 wherein:

X_3 is $=CH_2$

q is 0 or 1:

each J is independently selected from the group
25 consisting of -H, -OH, and -F, provided that when a
first and second J are bound to a C and said first J is
-OH, said second J is -H;

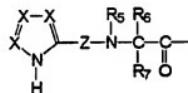
- 37 -

m is 0, 1, or 2;

T is -OH, -CO-CO₂H, -CO₂H or any bioisosteric replacement for -CO₂H;

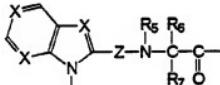
R₁ is selected from the group consisting of the
 5 following formulae, in which any ring may optionally be singly or multiply substituted at any carbon by Q₁, at any nitrogen by R₅, or at any atom by -O-, -OH-, -CO₂H, or halogen, any saturated ring may optionally be unsaturated at one or two bonds; and wherein R₁ (e) and
 10 R₁ (y) are optionally benzofused;

(a)



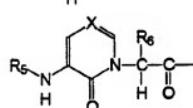
;

(b)



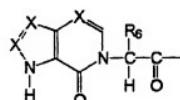
;

(c)



;

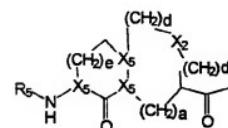
(d)



;

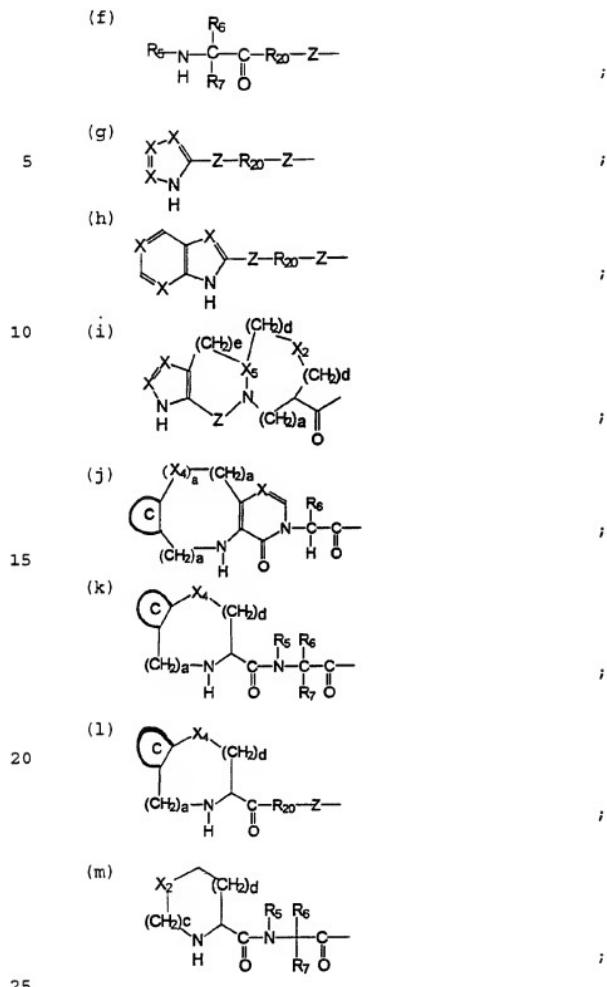
20

(e)

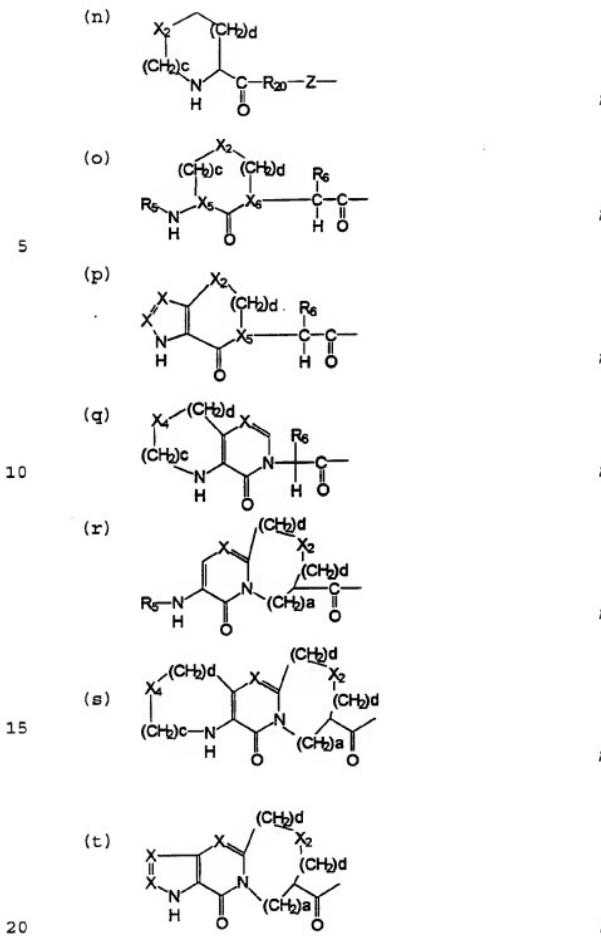


;

- 38 -

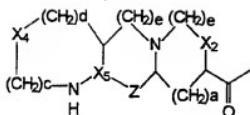


- 39 -



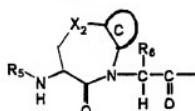
- 40 -

(v)

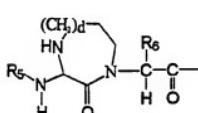


5

(w)

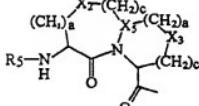


(x)



10

(y)

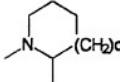
 R_{20} is selected from the group consisting of:

(aa1)



15

(aa2)



(aa3)



20

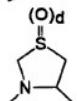
- 41 -

(aa4)



(aa5)

5



(bb)

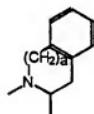


(cc)



10

(dd)

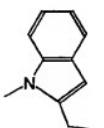


(ee)

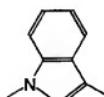
15



(ff)



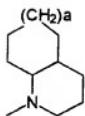
(gg)



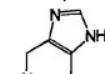
20

- 42 -

(gga)



(ggb)



5

; and

(ggc)



;

wherein each ring C is independently chosen from
 10 the group consisting of benzo, pyrido, thieno, pyrrolo,
 furano, thiazolo, isothiazolo, oxazolo, isoxazolo,
 pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

R₃ is

-CN,

15 -CH=CH-R₉,-CH=N-O-R₉,-(CH₂)₁₋₃-T₁-R₉,-CJ₂-R₉,-CO-R₁₃, or20 -CO-CO-N^{/R₅}
 \R₁₀;

each R₄ is independently selected from the group
 consisting of:

25 -H,
 -Ar₁,
 -R₉,
 -T₁-R₉, and

- 43 -

- (CH₂)_{1,2,3}-T₁-R₉,

each T₁ is independently selected from the group consisting of:

- 5 -CH=CH-,
- O-,
- S-,
- SO-,
- SO₂-,
- NR₁₀-,
- 10 -NR₁₀-CO-,
- CO-,
- O-CO-,
- CO-O-,
- CO-NR₁₀-,
- 15 -O-CO-NR₁₀-,
- NR₁₀-CO-O-,
- NR₁₀-CO-NR₁₀-,
- SO₂-NR₁₀-,
- NR₁₀-SO₂-, and
- 20 -NR₁₀-SO₂-NR₁₀-,

each R₅ is independently selected from the group consisting of:

- 25 -H,
- Ar₁,
- CO-Ar₁,
- SO₂-Ar₁,
- CO-NH₂,
- SO₂-NH₂,
- R₉,
- 30 -CO-R₉,
- CO-O-R₉,
- SO₂-R₉,

- 44 -

5 $\begin{array}{c} / \text{Ar}_1 \\ - \text{CO} - \text{N} \\ \backslash \text{R}_{10}, \end{array}$

$\begin{array}{c} / \text{Ar}_1 \\ - \text{SO}_2 - \text{N} \\ \backslash \text{R}_{10}, \end{array}$

$\begin{array}{c} / \text{R}_9 \\ - \text{CO} - \text{N} \\ \backslash \text{R}_{10}, \end{array}$ and

0 $\begin{array}{c} / \text{R}_9 \\ - \text{SO}_2 - \text{N} \\ \backslash \text{R}_{10}, \end{array}$

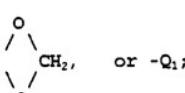
R₆ and R₇ taken together form a saturated 4-8 member carbocyclic ring or heterocyclic ring containing
15 -O-, -S-, or -NH-; or
R₇ is -H and R₆ is:
-H,
-Ar₁,
-R₉,
20 -(CH₂)_{1,2,3}-T₁-R₉, or
an α-amino acid side chain residue:

each R₉ is a C₁₋₆ straight or branched alkyl group optionally singly or multiply substituted by -OH, -F, or =O and optionally substituted with one or two Ar₁ groups;

each R₁₀ is independently selected from the group consisting of -H or a C₁₋₆ straight or branched alkyl group;

each R_{13} is independently selected from the group
30 consisting of -Ar₂, -R₄ and -N-OH
 |
 R₅

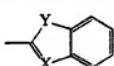
- 45 -

each Ar₁ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 5 carbon atoms and between 1 and 3 rings, said cycloalkyl group being optionally benzofused, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocycle group containing at least one heteroatom group selected from 10 -O-, -S-, -SO-, -SO₂-, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -NH₂, -CO₂H, 15 -Cl, -F, -Br, -I, -NO₂, -CN, =O, -OH, -perfluoro C₁₋₃ alkyl,
 
 or -Q₁;

20

each Ar₂ is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by -Q₁ and -Q₂:

25 (hh)



(ii)



30 (jj)



, and

(kk)



- 46 -

each Q₁ is independently selected from the group
consisting of

-Ar₁

-O-Ar₁

5 -R₉,

-T₁-R₉, and

- (CH₂)_{1,2,3}-T₁-R₉;

each Q₂ is independently selected from the group
consisting of -OH, -NH₂, -CO₂H, -Cl, -F, -Br, -I,

10 -NO₂, -CN, -CF₃, and



15 provided that when -Ar₁ is substituted with a Q₁
group which comprises one or more additional -Ar₁
groups, said additional -Ar₁ groups are not substituted
with Q₁;

each X is independently selected from the group
20 consisting of =N-, and =CH-;

each X₂ is independently selected from the group
consisting of -O-, -CH₂-, -NH-, -S-, -SO-, and -SO₂-;

each X₃ is independently selected from the group
consisting of -CH₂-, -S-, -SO-, and -SO₂-;

25 each X₄ is independently selected from the group
consisting of -CH₂- and -NH-;

each X₅ is independently selected from the group
consisting of -CH- and -N-;

- 47 -

X_6 is CH or N, provided that when X_6 is N in the R₁ group labeled (o) and X_5 is CH and X_2 is CH, the ring of the R₁ group labeled (o) must be substituted by Q; or benzofused;

5 each Y is independently selected from the group consisting of -O- and -S-, and -NH;

each Z is independently CO or SO₂,

each a is independently 0 or 1,

each c is independently 1 or 2,

10 each d is independently 0, 1, or 2, and

each e is independently 0, 1, 2, or 3,

provided that when

R₁ is (f),

R₆ is an α -amino acid side chain residue, and

15 R₇ is -H,

then (aa1) and (aa2) must be substituted with Q₁;

also provided that when

R₁ is (o),

g is 0,

20 J is -H,

m is 1,

R₆ is an α -amino acid side chain residue,

R₇ is -H,

X₂ is -CH₂-,

25 X₅ is -CH- ,

|

X₆ is -N- , and

|

- 48 -

R₃ is
-CO-N₁₀
R₁₀, or -CO-R₁₃, when

5 R₁₃ is:
-CH₂-O-CO-Ar₁,
-CH₂-S-CO-Ar₁,
-CH₂-O-Ar₁,
-CH₂-S-Ar₁, or
10 -R₄ when -R₄ is -H;

then the ring of the R₁(o) group must be substituted with Q₁ or benzofused; and

provided that when

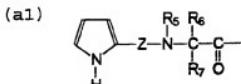
15 R₁ is (w),
g is 0,
J is -H,
m is 1,
T is -CO₂H or -CO-NH-OH,
X₂ is O,
20 R₅ is benzyloxycarbonyl, and
ring C is benzo,

then R₃ cannot be -CO-R₁₃ when:

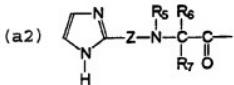
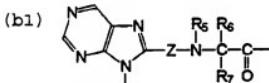
25 R₁₃ is -CH₂-O-Ar₁ and
Ar₁ is 1-phenyl-3-chloro- or
3-trifluoromethyl-pyrazole-5-yl;
or when
R₁₃ is -CH₂-O-CO-Ar₁ and
Ar₁ is 2,6-dichlorophenyl.

30 Preferred forms of the R₁ group (a) for
embodiments A and B are:

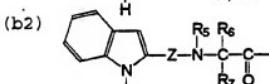
- 49 -



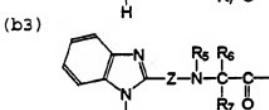
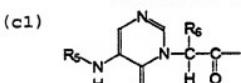
; and

Preferred forms of the R₁ group (b) are:

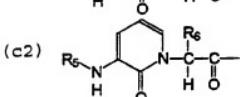
;



; and

Preferred forms of the R₁ group (c) are:

; and



;

provided that when R₁ is (c1),

g is 0,

J is -H,

m is 1,

T is -CO₂H,

X is N,

25 R₅ is benzyloxycarbonyl, andR₆ is -H,

- 50 -

then R₃ cannot be -CO-R₁₃ when
 R₁₃ is -CH₂-O-Ar₁ and
 Ar₁ is a chloro-substituted 1-phenyl-3-
 trifluoromethyl-pyrazole-5-yl, or when

5

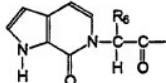
R₁₃ is -CH₂-O-CO-Ar₁ and
 Ar₁ is 2,6-dichlorophenyl,

and when the 2-position of the scaffold ring is
 substituted with para-fluoro-phenyl;

10

Preferred forms of the R₁ group (d) are:

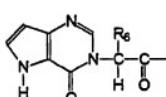
(d1)



;

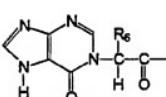
15

(d2)



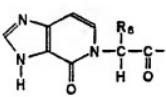
;

(d3)



; and

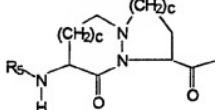
(d4)



20

Preferred forms of the R₁ group (e) are:

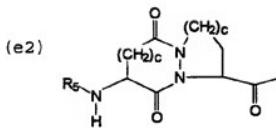
(e1)



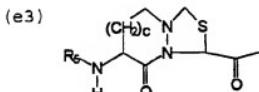
;

25

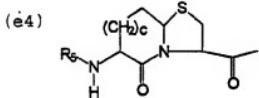
- 51 -



5

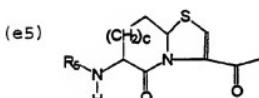


;

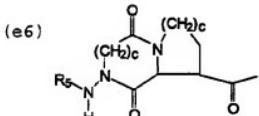


;

10

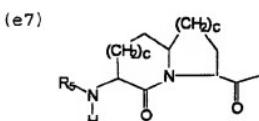


;



;

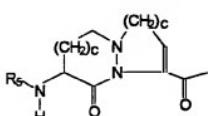
15



;

which is optionally benzofused;

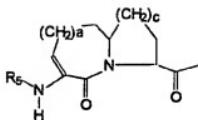
(e8)



; and

- 52 -

(e9)



provided that when R_1 is (e4),

5 g is 0,
 J is -H,
 m is 1,
 T is $-CO_2H$,
 R_5 is benzylloxycarbonyl, and
 10 c is 1,

then R_3 cannot be $-CO-R_{13}$ when
 R_{13} is $-CH_2-O-Ar_1$ and
 Ar_1 is 1-phenyl-3-trifluoromethyl-pyrazole-
 5-yl, wherein the phenyl is optionally substituted with
 15 a chlorine atom; or when
 R_{13} is $-CH_2-O-CO-Ar_1$ and
 Ar_1 is 2,6-dichlorophenyl,
 and when the 2-position of the scaffold ring is
 substituted with para-fluoro-phenyl; and

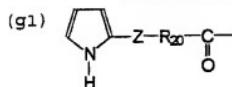
20 also provided that when
 R_1 is (e7),
 g is 0,
 J is -H,
 m is 1,
 25 T is $-CO_2H$ or $-CO-NH-OH$,
 R_5 is a protective group for the N atom of an
 amino acid side chain residue, and
 each c is 1,

then R_3 cannot be $-CO-R_{13}$ when
 30 R_{13} is:

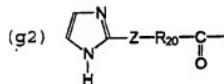
- 53 -

-CH₂-O-CO-Ar₁,
 -CH₂-S-CO-Ar₁,
 -CH₂-O-Ar₁, or
 -CH₂-S-Ar₁.

5 Preferred forms of the R₁ group (g) are:

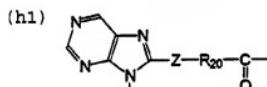


; and

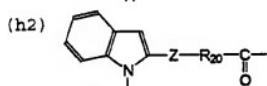


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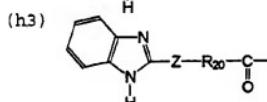
Preferred forms of the R₁ group (h) are:



;

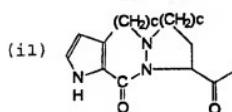


; and

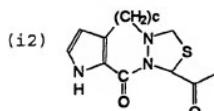


.

20 Preferred forms of the R₁ group (i) are:



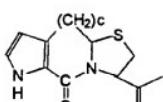
;



;

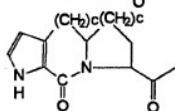
- 54 -

(i3)



; and

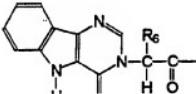
(i4)



5

Preferred forms of the R₁ group (j) are:

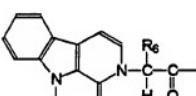
(j1)



;

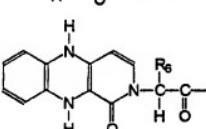
10

(j2)



;

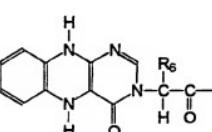
(j3)



; and

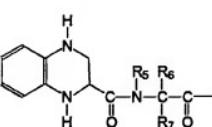
15

(j4)

Preferred forms of the R₁ group (k) are:

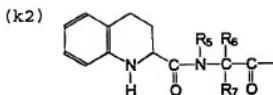
20

(k1)

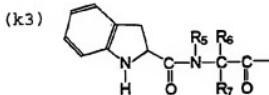


;

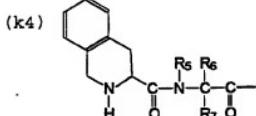
- 55 -



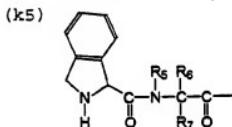
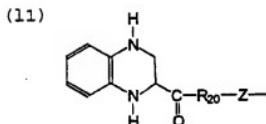
5



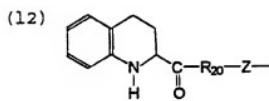
10



; and

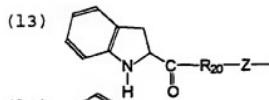
Preferred forms of the R₁ group (1) are:

15

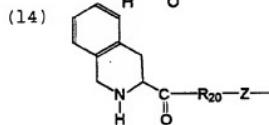


;

20

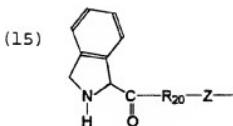


;

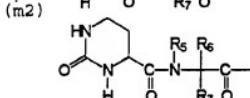
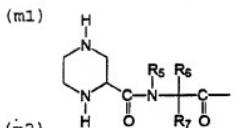


; and

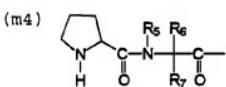
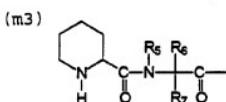
- 56 -



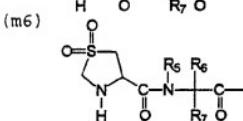
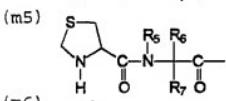
5

Preferred forms of the R₁ group (m) are:

10



15



;

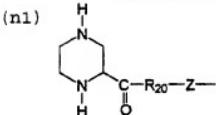
;

;

;

; and

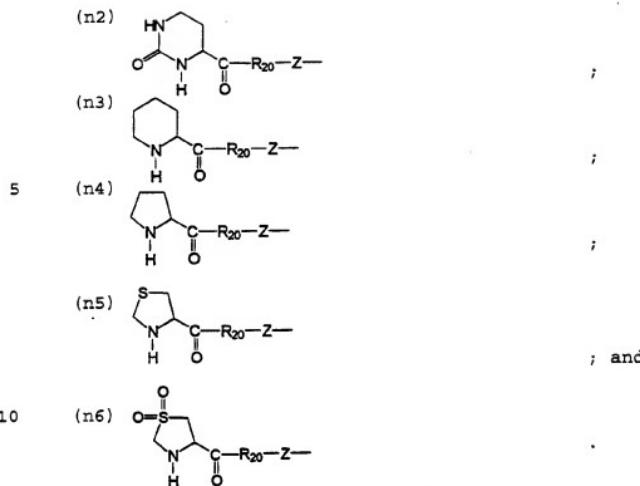
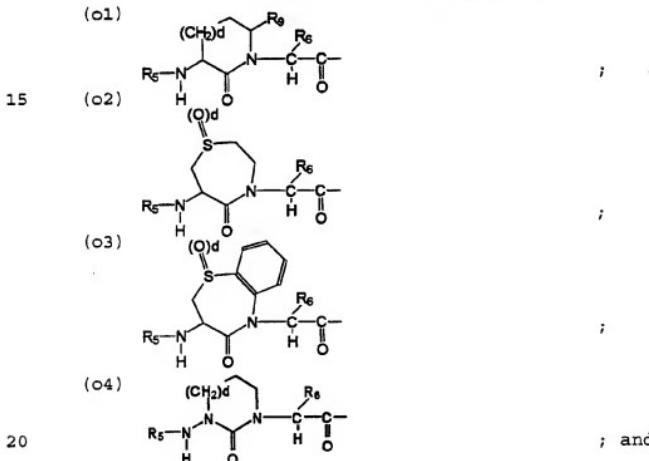
.

Preferred forms of the R₁ group (n) are:

20

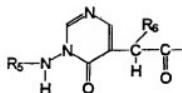
;

- 57 -

Preferred forms of the R₁ group (o) are:

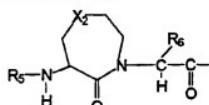
- 58 -

(o5)



5 A preferred form of the R₁ group (o) of embodiment B is:

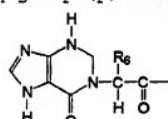
(o6)



wherein X₂ is -O-, -S-, -SO₂-, or -NH-.

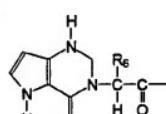
10 For embodiments A and B, preferred forms of the R₁ group (p) are:

(p1)

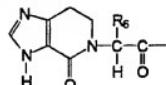


15

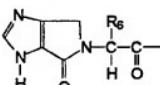
(p2)



(p3)

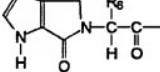


(p4)



20

(p5)

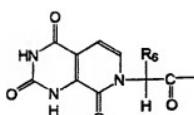


; and

- 59 -

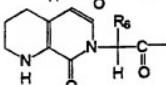
Preferred forms of the R₁ group (q) are:

(q1)



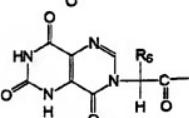
;

(q2)



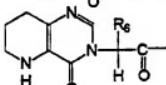
;

(q3)



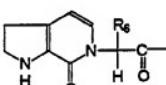
;

(q4)



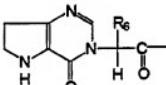
;

10 (q5)



; and

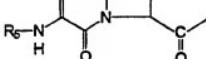
(q6)



15

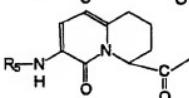
Preferred forms of the R₁ group (r) are:

(r1)



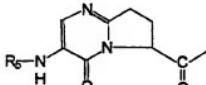
;

(r2)



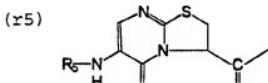
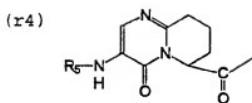
;

20 (r3)



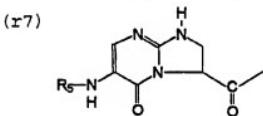
;

- 60 -

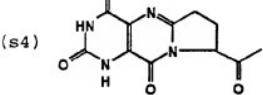
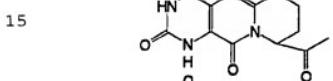
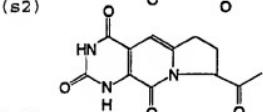
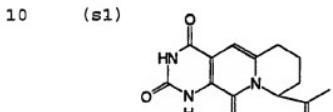


5 (x6)

; and

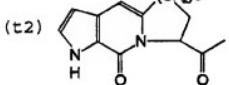
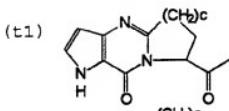


Preferred forms of the R₁ group (s) are:



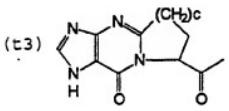
- 61 -

Preferred forms of the R₁ group (t) are:

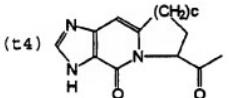


5

;

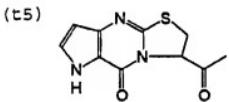


;

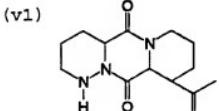


; and

10

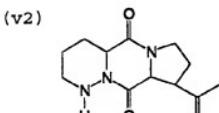


Preferred forms of the R₁ group (v) are:



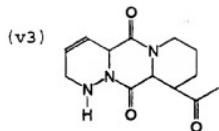
15

;

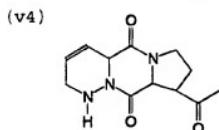


;

- 62 -



; and

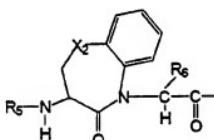


5

A preferred form of the R1 group (w) of embodiment B is:

(w1)

10



wherein X₂ is -O-, -S-, -SO₂- or -NH-.

The preferred compounds of embodiments A and B of this invention are those which employ formula α, wherein:

15

X₁ is CH;

g is O;

J is -H;

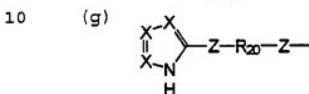
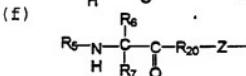
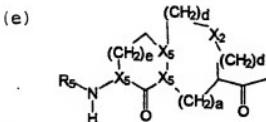
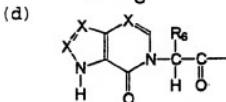
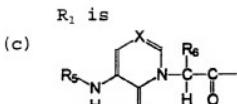
m is 0 or 1 and T is -Ar₃, -CO-CO₂H, -CO₂H or any bioisosteric replacement for -CO₂H, or

20

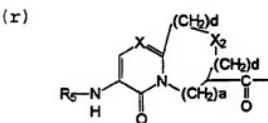
m is 1 or 2 and T is -OH, -CF₃, or -CO₂H;

more preferably m is 1 and T is -CO₂H;

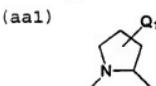
- 63 -



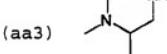
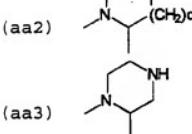
, or



15

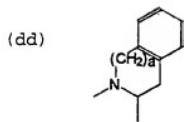
R₂₀ is

20



, or

- 64 -



wherein ring C is benzo;

R₃ is

- 5 -CO-R₁₃, or
 /R₅
 -CO-CO-N
 \R₁₀;

most preferably R₃ is any one of 1), 2) or 3) as follows: 1) -CO-Ar₂, 2) -CO-R₉ where R₉ is C₃₋₆ alkyl substituted with two Ar₁ groups or one Ar₁ group itself substituted with an Ar₁ group, -C₁₋₂-Ar₁, -Cl, -CH₃, or -CF₃, or 3) -(CH₂)₁₋₂-T₁-R₉ where T₁ is -O- or -S- and R₉ is C₁₋₂ alkyl substituted with two Ar₁ groups or one Ar₁ group itself substituted with an Ar₁ group, C₁₋₂-Ar₁, -Cl, -CH₃, or -CF₃;

R₄ is -H or -R₉;

T₁ is

- 20 -O-,
 -S-,
 -CO-,
 -O-CO-, or
 -SO₂-;

when R₁ is (a), (b), (k), or (m), R₅ is preferably -Ar₁ or C₁₋₄-Ar₁;

- 65 -

when R₁ is (c), (e), (f), (o), or (r), R₅ is preferably -SO₂-Ar₁, -SO₂-R₆, or -CO-C₁₋₄-Ar₁;

R₇ is -H and R₆ is C₁₋₄-Ar₁;

5 R₁₀ is -H or a C₁₋₃ straight or branched alkyl group;

R₁₃ is -Ar₂;

Ar₁ is phenyl, naphthyl, pyridyl, benzothiazolyl, thienyl, benzothienyl, benzoxazolyl, 2-indanyl, or indolyl;

10 Ar₂ is preferably substituted with -Ar₁, or -C₁₋₄-Ar₁;

Ar₃ is phenyl, thiophene, thiazole, pyridine, or oxazole; and

15 Q₁ is -R₉ or -(CH₂)₁₋₂-T₁-(CH₂)₁₋₃-Ar₁ where T₁ is -O- or -S-.

In connection with this continuation-in-part, we now prefer the compounds of embodiment B of this invention which employ formula g, wherein:

X₁ is -CH₃;

20 g is O;

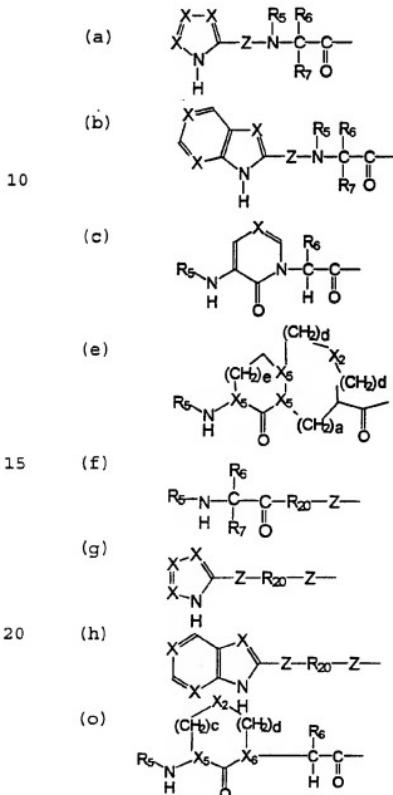
J is -H;

m is 0 or 1 and T is -CO-CO₂H, or any bioisosteric replacement for -CO₂H; or

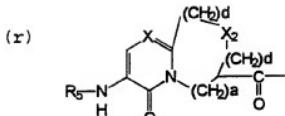
- 66 -

m is 1 and T is $-CO_2H$;

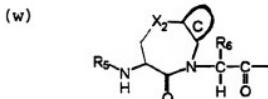
R₁ is selected from the group consisting of the following formulae, in which any ring may optionally be singly or multiply substituted at any carbon by Q₁ at 5 any nitrogen by R₅, or at any atom by =O, -OH, -CO₂H, or halogen, and wherein (e) is optionally benzofused:



- 67 -



, or



5

;

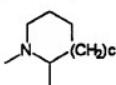
 R_{20} is

(aa1)



, or

(aa2)



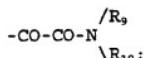
10

and c is 1;

ring C is benzo optionally substituted with
 $-C_{1-3}$ alkyl, $-O-C_{1-3}$ alkyl, $-Cl$, $-F$ or $-CF_3$;

 R_3 is:

15

 $-CO-R_{13}$, or

more preferably R_3 is any one of 1), 2) or 3) as follows: 1) $-CO-Ar_2$; 2) $-CO-R_9$, where R_9 is C_{1-5} alkyl substituted with an Ar_1 ; or 3) $-CH_2-T_1-R_9$, where T_1 is $-O-$ or $-S-$ and R_9 is C_{1-2} alkyl substituted with one Ar_1 group;

 R_4 is $-H$ or $-R_9$;

- 68 -

T₁ is:

- O-,
- S-,
- CO-,
- 5 -O-CO-, or
- SO₂-;

when R₁ is (a) or (b), R₅ is preferably -H, and
when R₁ is (c), (e), (f), (o), (r), (w), (x) or
(y), R₅ is preferably:

- 10 -CO-Ar₁
- SO₂-Ar₁,
- CO-NH₂,
- CO-NH-Ar₁,
- CO-R₉,
- 15 -CO-O-R₉,
- SO₂-R₉, or
- CO-NH-R₉,

R₇ is -H and R₆ is
20 -H,
-R₉ or
-Ar₁;

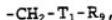
R₉ is C₁₋₆ straight or branched alkyl group
optionally substituted with =O and optionally
25 substituted with -Ar₁;

R₁₀ is -H or a C₁₋₃ straight or branched alkyl
group;

R₁₃ is:

- 30 -H,
- R₉,
- Ar₂, or

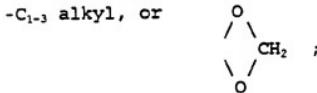
- 69 -



more preferably where -Ar_2 is
 (hh) and where (hh) is optionally substituted singly or
 multiply with $-\text{C}_{1-6}$ alkyl, $-\text{O-C}_{1-6}$ alkyl,
 5 $-\text{NH-C}_{1-6}$ alkyl, $-\text{N-(C}_{1-6}\text{ alkyl)}_2$, $-\text{S-C}_{1-6}$ alkyl, $-\text{Cl}$,
 $-\text{F}$, $-\text{CF}_3$, or



10 Ar_1 is phenyl, naphthyl, pyridyl, benzothiazolyl,
 thiienyl, benzothienyl, benzoxazolyl, 2-indanyl, or
 indolyl substituted with $-\text{O-C}_{1-3}$ alkyl, $-\text{NH-C}_{1-3}$ alkyl, $-\text{C}_{1-3}$
 15 $-\text{(C}_{1-3}\text{ alkyl)}_2$, $-\text{Cl}$, $-\text{F}$, $-\text{CF}_3$,
 $-\text{C}_{1-3}$ alkyl, or



20

preferably where Ar_2 is:

(iii)



(jj)



25

, or

(kk)



each X is independently selected from the group
 30 consisting of =N-, and =CH-;

- 70 -

each X_2 is independently selected from the group consisting of -O-, -CH₂-, -NH-, -S-, -SO-, and -SO₂-;

each X_5 is independently selected from the group consisting of -CH- and -N-;

5

| |

X_6 is -CH- or -N-; and

| |

Z is C=O;

10 provided that when

R₁ is (f),

R₆ is an α -amino acid side chain residue, and

R₇ is -H,

then (aa1) and (aa2) must be substituted with Q₁;

15

also provided that when

R₁ is (o),

g is 0,

J is -H,

20 m is 1,

R₆ is an α -amino acid side chain residue,

R₇ is -H,

X₂ is -CH₂-,

X₅ is -CH-,

|

25

X_6 is -N-, and

|

30 R₃ is

$\begin{array}{c} /R_{10} \\ -CO-N \\ \backslash R_{10} \end{array}$, or
-CO-R₁₃, when

35

- 71 -

R₁₃ is:

- CH₂-O-CO-Ar₁,
- CH₂-S-CO-Ar₁,
- CH₂-O-Ar₁,
- CH₂-S-Ar₁, or
- 5 -R₄ when -R₄ is -H;

then the ring of the R₁(o) group must be substituted with Q₁ or benzofused; and

provided that when

- 10 R₁ is (w),
g is 0,
J is -H,
m is 1,
T is -CO₂H,
- 15 X₂ is O,
R₅ is benzyloxycarbonyl, and
ring C is benzo,
then R₃ cannot be -CO-R₁₃ when:
R₁₃ is -CH₂-O-Ar₁ and
Ar₁ is 1-phenyl-3-trifluoromethyl-pyrazole-5-yl,
wherein the phenyl is optionally substituted with a chlorine atom;
or when R₁₃ is -CH₂-O-CO-Ar₁, wherein
Ar₁ is 2,6-dichlorophenyl.

25 A preferred form of R₁₃ is -CH₂-O-R₉, wherein R₉ is a C₁₋₆ straight or branched alkyl group optionally substituted with =O and optionally substituted with Ar₁;

30 another preferred form of R₁₃ is CH₂-S-R₉, wherein R₉ is a C₁₋₆ straight or branched alkyl group optionally substituted with Ar₁;

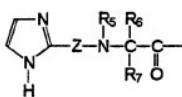
- 72 -

another preferred form of R₁₃ is CH₂-O-R₉, wherein R₉ is a C₁₋₆ straight or branched alkyl group optionally substituted with Ar₁;

another preferred form of R₁₃ is H.

5 A more preferred form of the R₁ group (a) is:

(a2)



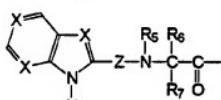
optionally substituted with Q₁, wherein
R₅ is -H;

R₇ is -H; and

10 Z is C=O;

a more preferred form of the R₁ group (b) is:

(b)



optionally substituted with Q₁, wherein

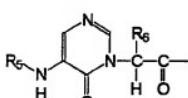
R₅ is -H;

15 R₇ is -H; and

Z is C=O;

more preferred forms of the R₁ group (c) are:

(c1)

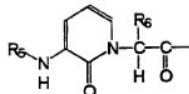


20

, and

- 73 -

(c2)

provided that when R₁ is (c1),

g is 0,

5 J is -H,

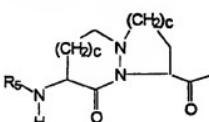
m is 1,

T is -CO₂H,

X is N,

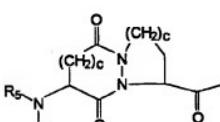
R₅ is benzyloxycarbonyl, and10 R₆ is -H,then R₃ cannot be -CO-R₁₃ whenR₁₃ is -CH₂-O-Ar₁ andAr₁ is 1-phenyl-3-trifluoromethyl-pyrazole-5-yl wherein the phenyl is optionally substituted with
15 a chlorine atom; or whenR₁₃ is -CH₂-O-CO-Ar₁, whereinAr₁ is 2,6-dichlorophenyl,and wherein the 2-position of the scaffold ring is
substituted with para-fluoro-phenyl;20 more preferred forms of the R₁ group (e) are:

(e1)



, and

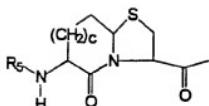
(e2)



25 wherein c is 2; and

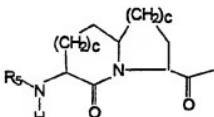
- 74 -

(e4)



, and

(e7)



5

which is optionally
benzofused,

wherein c is 1 or 2;

provided that when R₁ is (e4),

10

g is 0,

J is -H,

m is 1,

T is -CO₂H,R₅ is benzyloxycarbonyl, and

15

c is 1,

then R₁ cannot be -CO-R₃ when

R₁₃ is -CH₂-O-Ar₁ and

Ar₁ is 1-phenyl-3-trifluoromethyl-pyrazole-5-yl wherein the phenyl is optionally substituted with
20 a chlorine atom; or when

R₁₃ is -CH₂-O-CO-Ar₁, whereinAr₁ is 2,6-dichlorophenyl,

and wherein the 2-position of the scaffold ring is substituted with para-fluoro-phenyl; and

25

also provided that when

R₁ is (e7),

g is 0,

J is -H,

m is 1,

- 75 -

T is $\text{-CO}_2\text{H}$, -CO-NH-OH , or a bioisosteric replacement for $\text{-CO}_2\text{H}$,

R₅ is a protective group for the N atom of an α -amino acid side chain residue, and
each c is 1,

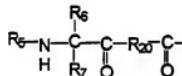
5

then R₃ cannot be -CO-R_{13} when
R₁₃ is:

10

$\text{-CH}_2\text{-O-CO-Ar}_1$,
 $\text{-CH}_2\text{-S-CO-Ar}_1$,
 $\text{-CH}_2\text{-O-Ar}_1$, or
 $\text{-CH}_2\text{-S-Ar}_1$.

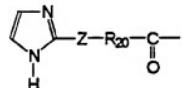
a more preferred form of the R₁ group (f) is
(f1)



15

a more preferred form of the R₁ group (g) is:

(g2)



; wherein

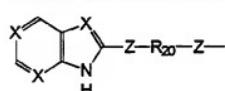
R₂₀ is (aa1) optionally substituted singly or multiply with Q₁; and

20

Z is C=O;

a more preferred form of the R₁ group (h) is:

(h)



; wherein

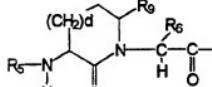
- 76 -

R_{20} is (aa1) optionally substituted singly or multiply with Q_1 ; and

Z is C=O;

more preferred forms of the R_1 group (o) are:

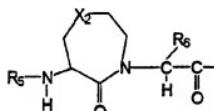
5 (o1)



;

wherein d is 1 or 2; and

(o6)

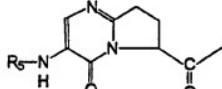


;

10

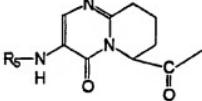
more preferred forms of the R_1 group (r) are:

(r3)



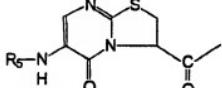
;

(r4)



; and

15 (r5)

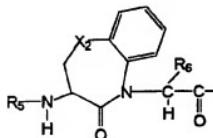


optionally substituted with Q_1 ;

- 77 -

a more preferred form of the R₁ group (w) is:

(w1)



; wherein

X₂ is:

- 5 -NH-,
 -S-,
 -O-, or
 -SO₂-;

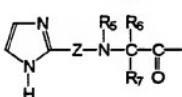
optionally substituted with R₅ or Q₁ at X₂

10 when X₂ is -N-; and

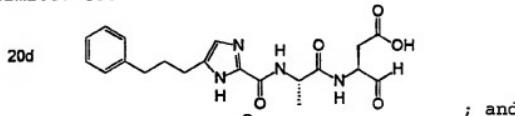
ring C is benzo substituted with -C₁-, alkyl,
 -O-C₁-, alkyl, -Cl, -F or -CF₃.

When R₁ is:

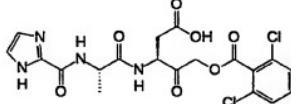
(a2)



15 preferred compounds of this invention include but are
 not limited to:



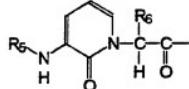
142



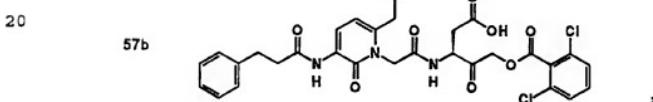
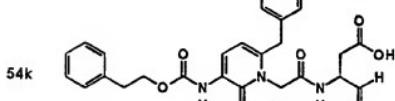
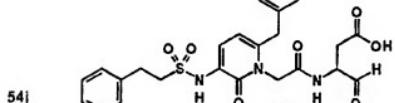
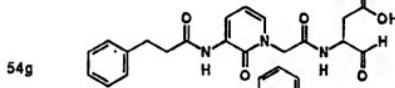
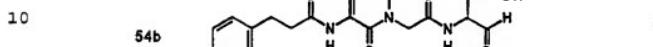
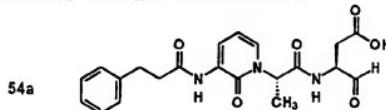
- 78 -

A preferred compound of embodiment B of this invention employs formula α , wherein the R₁ is:

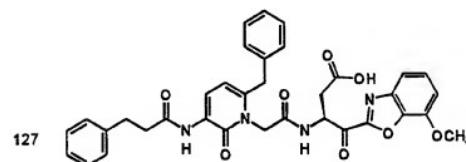
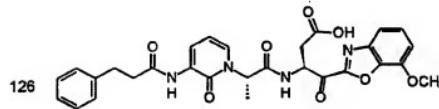
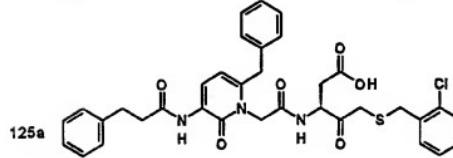
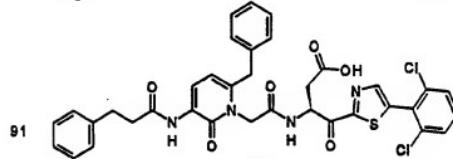
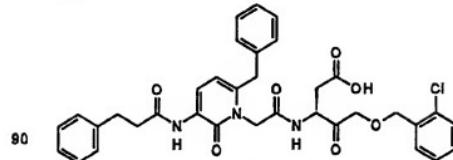
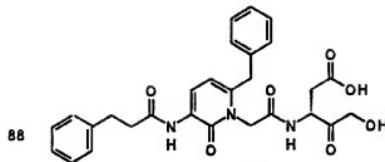
(c2)



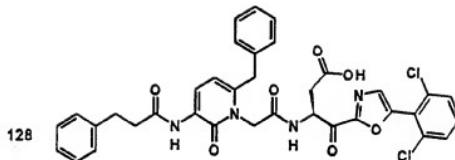
Preferred compounds of this embodiment include but are not limited to:



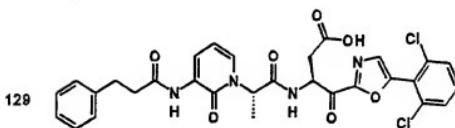
- 79 -



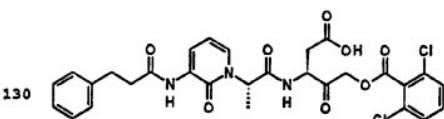
- 80 -



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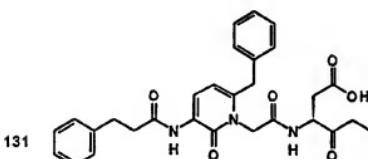


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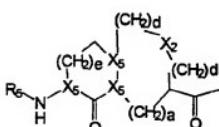


; and

15

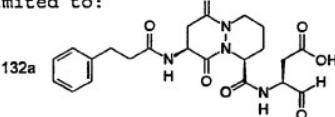
When R₁ is:

(e)

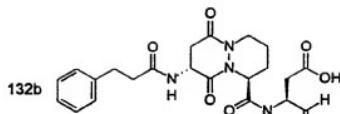


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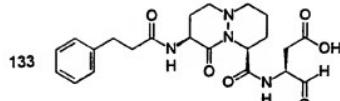
preferred compounds of this invention include but are not limited to:



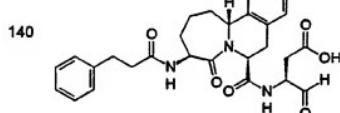
- 81 -



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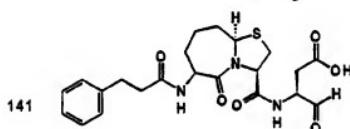


10



; and

15

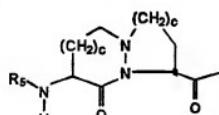


A preferred compound of embodiment B of this invention employs formula α , wherein:

20

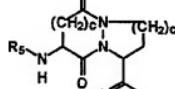
 R_1 is:

(e1)



, or

(e2)



25

and c is 2;

30

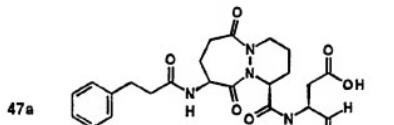
 m is 1;

- 82 -

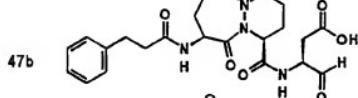
T is $\text{-CO}_2\text{H}$; andR₃ is -CO-R_{13} .

Preferred compounds of this embodiment
include but are not limited to:

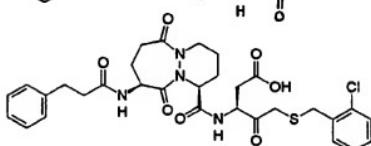
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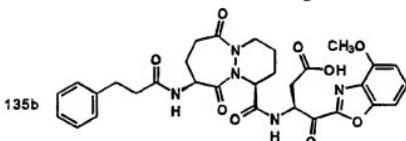
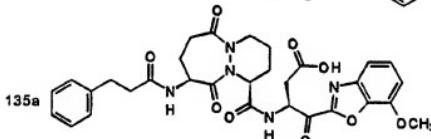
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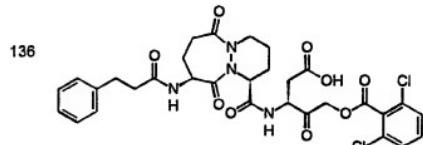
125b



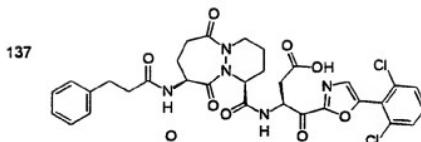
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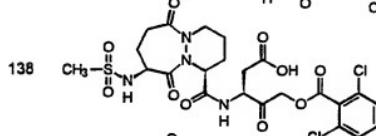
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- 83 -

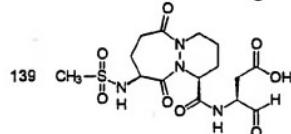


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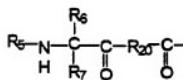


; and

10

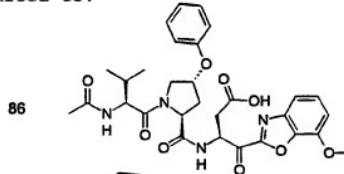
When R₁ is:

15 (f1)

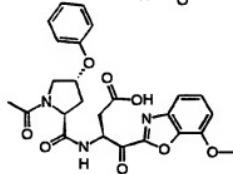


preferred compounds of this invention include but are not limited to:

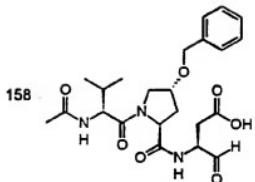
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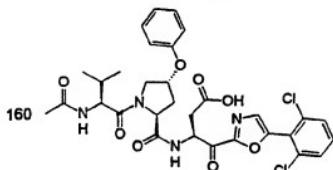
87



- 84 -



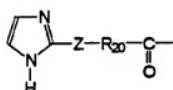
i and



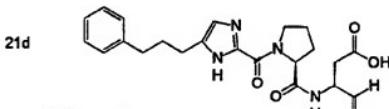
10

When R_3 is:

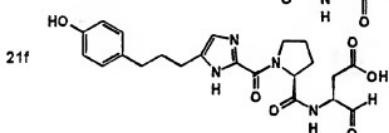
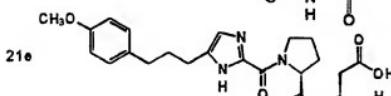
(92)



15 preferred compounds of this invention include but are
not limited to:

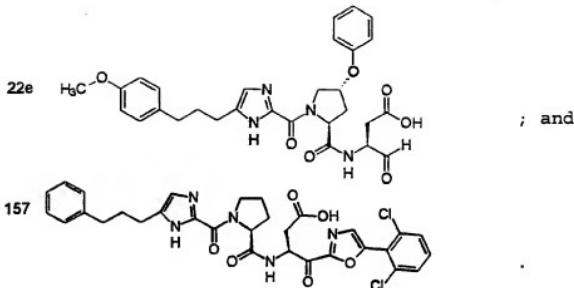


-1-



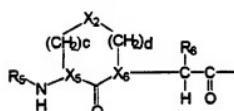
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- 85 -

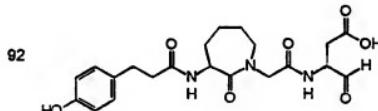


When R₁ is:

(a)



preferred compounds of this invention include but are not limited to:

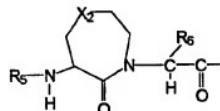


A preferred compound of embodiment B of this invention employs formula g, wherein:

R₁ is:

20

(86)

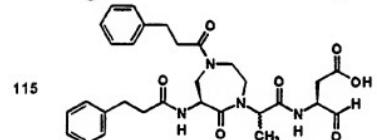
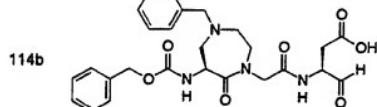
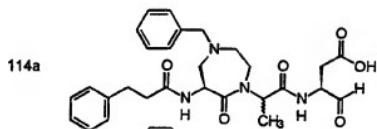


X_2 is $-\text{NH-}$;

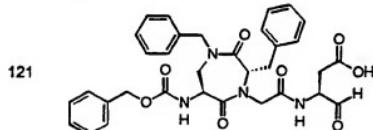
- 86 -

m is 1;
T is -CO₂H;
R₃ is -CO-R₁₃.

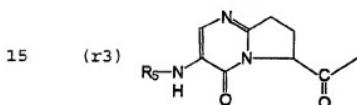
Preferred compounds of this embodiment
5 include but are not limited to:



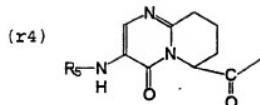
10 ; and



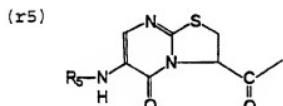
When R₁ is:



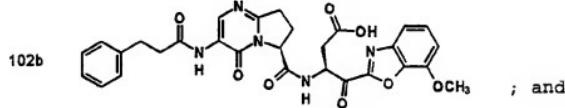
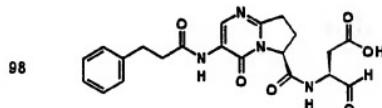
- 87 -



; or

5 optionally substituted with Q₁;

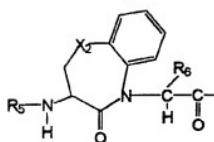
preferred compounds of embodiment B of this invention include but are not limited to:



- 88 -

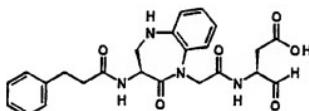
When R₁ is:

(w1)



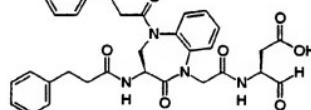
5 preferred compounds of this invention include but are not limited to:

106a



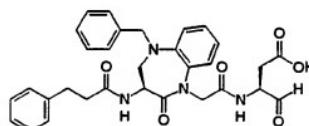
10

106b



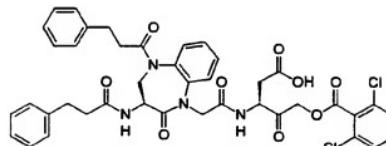
15

106c



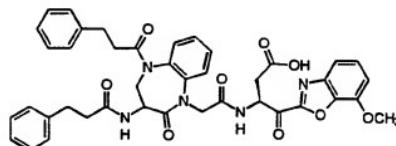
20

108a



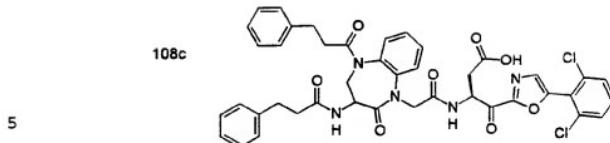
25

108b

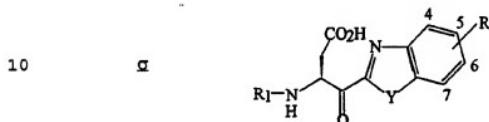


; and

- 89 -



The ICE inhibitors of another embodiment (C) of this invention are represented by the formula α :



wherein the ring is optionally substituted with one or more R groups, preferably 0, 1 or 2; and wherein:

R₁ is R₅-(A)_p-;

15 R₅ is selected from the group consisting of:

-H,

-Ar₁,

-CO-Ar₁,

-SO₂-Ar₁,

20 -R₉,

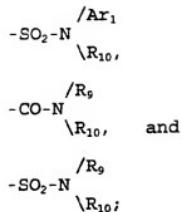
-CO-R₉,

-CO-O-R₉,

-SO₂-R₉,

25 -CO-N
 /Ar₁
 \R₁₀,

- 90 -



10

each A is independently selected from the group
consisting of any α -amino acid;

p is 0, 1, 2, 3 or 4;

Y is:

15

-O-,
-S- or
-NH;

R is:

20

-H,
-O-C₁₋₆ alkyl,
-NH(C₁₋₆ alkyl),
-N(C₁₋₆ alkyl)₂,
-S-C₁₋₆ alkyl,
-C₁₋₆ alkyl, or
-Q₂;

25

each R₉ is a C₁₋₆ straight or branched alkyl group
optionally singly or multiply substituted by -OH, -F,
or =O and optionally substituted with one or two Ar₁
groups;

30

each R₁₀ is independently selected from the group
consisting of -H or a C₁₋₆ straight or branched alkyl
group;

- 91 -

each T_1 is independently selected from the group consisting of:

- CH=CH-,
- O-,
- 5 -S-,
- SO-,
- SO₂-,
- NR₁₀-,
- NR₁₀-CO-,
- 10 -CO-,
- O-CO-,
- CO-O-,
- CO-NR₁₀-,
- O-CO-NR₁₀-,
- 15 -NR₁₀-CO-O-,
- NR₁₀-CO-NR₁₀-,
- SO₂-NR₁₀-,
- NR₁₀-SO₂-, and
- NR₁₀-SO₂-NR₁₀-,

- 20 each Ar_1 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 15 carbon atoms and between 1 and 3 rings, said 25 cycloalkyl group being optionally benzofused, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocycle group containing at least one heteroatom group selected from -O-, -S-, -SO-, -SO₂-, =N-, and -NH-, said heterocycle 30 group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by: -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂,

- 92 -

-CN, =O, -OH, -perfluoro C₁₋₃ alkyl,  or -Q₁;

each Q_i is independently selected from the group consisting of:

$$-Ax_1$$

$$-R_{\theta_1}$$

$$-T_1-R_9,$$

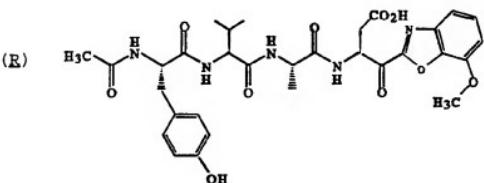
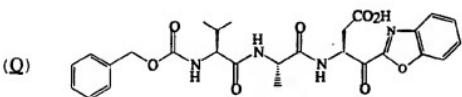
$$-(CH_2)_{1,2,3}-T_1-R_9;$$

each Q_2 is independently selected from the group consisting of -OH, -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂.

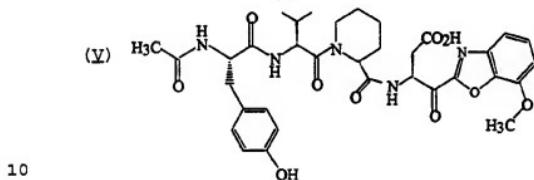
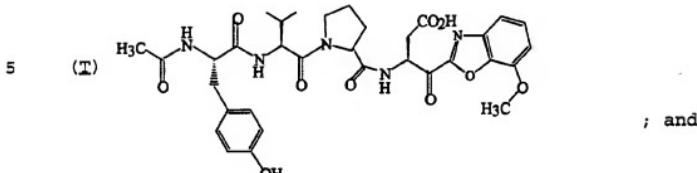
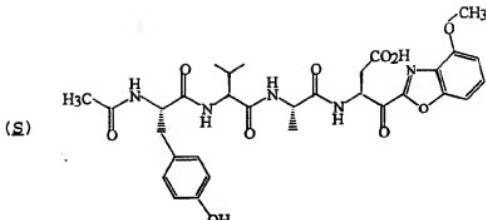
15 -CN, -CF₃, and 

20 provided that when -Ar₁ is substituted with a Q₁ group which comprises one or more additional -Ar₁ groups, said additional -Ar₁ groups are not substituted with Q₁.

Preferred compounds of embodiment C of this invention include but are not limited to:



- 93 -



10

Preferred compounds of embodiment C of this invention are also those in which each A is independently selected from the group consisting of the α -amino acids:

- 15 alanine,
- histidine,
- lysine,
- phenylalanine,
- proline,
- tyrosine,
- 20 valine,

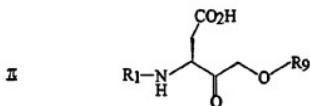
20

- 94 -

leucine,
isoleucine,
glutamine,
methionine,
homoproline,
5
3-(2-thienyl) alanine, and
3-(3-thienyl) alanine.

The ICE inhibitors of another embodiment (D)
of this invention are represented by the formula π :

10



wherein:

R_1 is $\text{R}_5-(\text{A})_p-$;

each T_1 is independently selected from the group
15 consisting of:

-CH=CH-,
-O-,
-S-,
-SO-,
20 -SO₂-,
-NR₁₀-,
-NR₁₀-CO-,
-CO-,
-O-CO-,
25 -CO-O-,
-CO-NR₁₀-,
-O-CO-NR₁₀-,
-NR₁₀-CO-O-,

- 95 -

-NR₁₀-CO-NR₁₀-,
-SO₂-NR₁₀-,
-NR₁₀-SO₂-,
and
-NR₁₀-SO₂-NR₁₀-;

5 R₅ is selected from the group consisting of:

-H,
-Ar₁,
-CO-Ar₁,
-SO₂-Ar₁,
10 -R₉,
-CO-R₉,
-CO-O-R₉,
-SO₂-R₉,
15 -CO-N^{/Ar₁}
^{\R₁₀},
-SO₂-N^{/Ar₁}
^{\R₁₀},
20 -CO-N^{/R₉}
^{\R₁₀}, and
25 -SO₂-N^{/R₉}
^{\R₁₀};

each A is independently selected from the group
consisiting of any α -amino acid;

p is 0, 1, 2, 3 or 4;

30 each R₉ is a C₁₋₆ straight or branched alkyl group
optionally singly or multiply substituted by -OH, -F,
or =O and optionally substituted with an Ar₁ group;

each R₁₀ is independently selected from the group

- 96 -

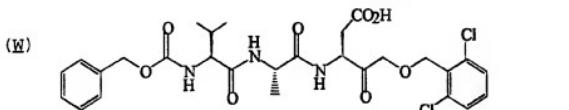
consisting of -H or a C₁₋₆ straight or branched alkyl group;

Ar₁ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 5 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 15 carbon atoms and between 1 and 3 rings, said cycloalkyl group being optionally benzofused, and a heterocycle group containing between 5 and 15 ring atoms and between 1 10 and 3 rings, said heterocycle group containing at least one heteroatom group selected from -O-, -S-, -SO-, -SO₂-, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, 15 and said cyclic group optionally being singly or multiply substituted by -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂, -CH₃, =O, -OH, -perfluoro C₁₋₃ alkyl, or

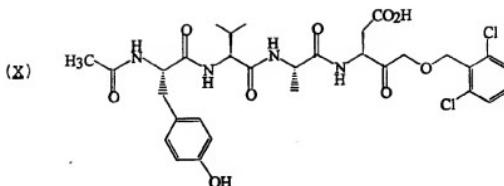


Preferred compounds of embodiment D of this 25 invention are those in which R₉ is a C₁₋₄ straight or branched alkyl substituted with Ar₁ when Ar₁ is phenyl.

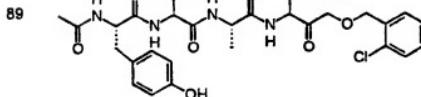
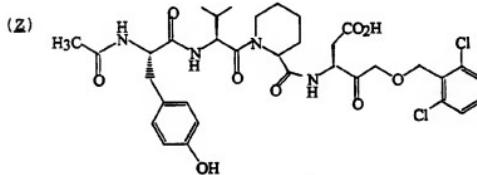
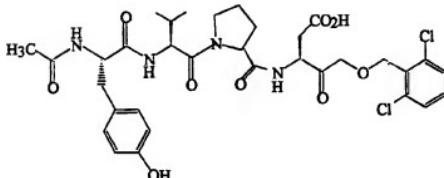
Preferred compounds of embodiment D of this invention include but are not limited to:



- 97 -



5 (Y)



10

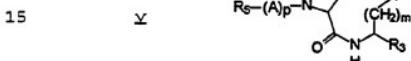
Preferred compounds of embodiment D of this invention are also those in which A is independently selected from the group consisting of the α -amino acids:

alanine,
histidine,

- 98 -

lysine,
phenylalanine,
proline,
tyrosine,
5
valine,
leucine,
isoleucine,
glutamine,
methionine,
10
homoproline,
3-(2-thienyl) alanine, and
3-(3-thienyl) alanine.

The ICE inhibitors of another embodiment (E) of this invention are represented by formula V:



wherein:

m is 0, 1, or 2;

20 T is -CO₂H, or any bioisosteric replacement for -CO₂H,

R₃ is
-CN,
-COR₁₃, or
25 -COCO-N₂
 /R₅
 \R₁₀,

R₅ is selected from the group consisting of:

- 99 -

-H,
-Ar₁,
-CO-Ar₁,
-SO₂-Ar₁,
5 -R₉,
-CO-R₉,
-CO-O-R₉,
-SO₂-R₉,
-CO-N₁₀<sup>/Ar₁
10 \R₁₀,
-SO₂-N₁₀^{/Ar₁}
 \R₁₀,
15 -CO-N₁₀^{/R₉}
 \R₁₀, and
-SO₂-N₁₀^{/R₉}
20 \R₁₀;</sup>

each A is independently selected from the group consisting of any α -amino acid;

p is 2 or 3;

25 each R₉ is a C₁₋₆ straight or branched alkyl group optionally singly or multiply substituted by -OH, -F, or =O and optionally substituted with one Ar₁ group;

each T₁ is independently selected from the group consisting of:

30 -CH=CH-,
-O-,
-S-,
-SO-,

- 100 -

-

SO₂- ,
-NR₁₀- ,
-NR₁₀-CO- ,
-CO- ,
5 -O-CO- ,
-CO-O- ,
-CO-NR₁₀- ,
-O-CO-NR₁₀- ,
-NR₁₀-CO-O- ,
10 -NR₁₀-CO-NR₁₀- ,
-SO₂-NR₁₀- ,
-NR₁₀-SO₂- , and
-NR₁₀-SO₂-NR₁₀ ;

15 each R₁₀ is independently selected from the group
consisting of -H or a -C₁₋₆ straight or branched alkyl
group;

each R₁₃ is independently selected from the group
consisting of H, R₉, Ar₂, and CH₂T₁R₉;

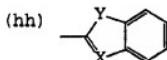
20 each Ar₁ is a cyclic group independently selected
from the set consisting of an aryl group which contains
6, 10, 12, or 14 carbon atoms and between 1 and 3
rings, a cycloalkyl group which contains between 3 and
15 carbon atoms and between 1 and 3 rings, said
25 cycloalkyl group being optionally benzofused, and a
heterocycle group containing between 5 and 15 ring
atoms and between 1 and 3 rings, said heterocycle group
containing at least one heteroatom group selected from
-O-, -S-, -SO-, -SO₂-, =N-, and -NH-, said heterocycle
30 group optionally containing one or more double bonds,
said heterocycle group optionally comprising one or
more aromatic rings, and said cyclic group optionally
being singly or multiply substituted by -NH₂, -CO₂H,

- 101 -

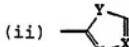
-Cl, -F, -Br, -I, -NO₂, -CN, =O, -OH,

-perfluoro C₁₋₃ alkyl, / \ O
 5 CH₂, or -Q₁; and
 \ / O

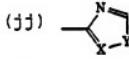
each Ar₂ is independently selected from the
 following group, in which any ring may optionally be
 10 singly or multiply substituted by -Q₁ and -Q₂:



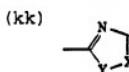
;



;



; and



;

15

each Q₁ is independently selected from the group
 20 consisting of:

-Ar₁

-O-Ar₁

-R₉,

-T₁-R₉, and

25 - (CH₂)_{1,2,3}-T₁-R₉;

each Q₂ is independently selected from the group
 consisting of -OH, -NH₂, -CO₂H, -Cl, -F, -Br, -I,

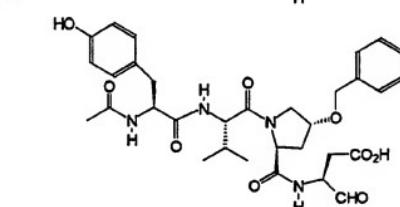
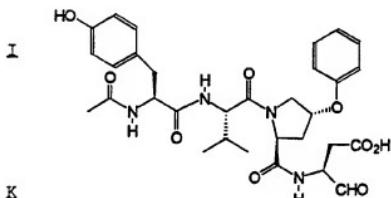
30 -NO₂, -CN, -CF₃, and / \ O
 CH₂;
 \ / O

35 provided that when -Ar₁ is substituted with a Q₁

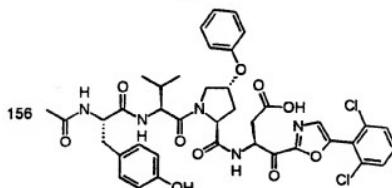
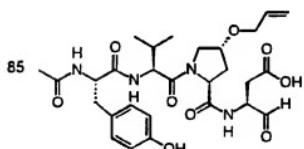
- 102 -

group which comprises one or more additional -Ar₁ groups, said additional -Ar₁ groups are not substituted with Q₁.

Preferred compounds of embodiment E of this
5 invention include but are not limited to:



10



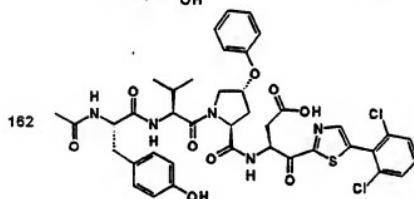
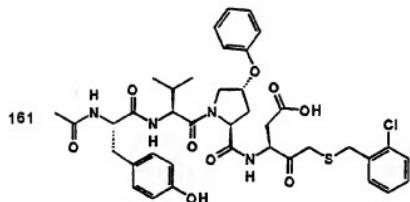
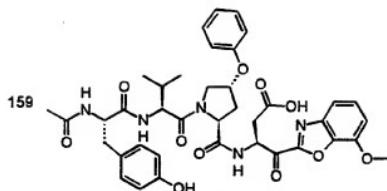
;

;

;

;

- 103 -



5

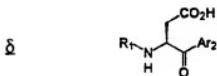
Preferred compounds of embodiment E of this invention are also those in which A is independently selected from the group consisting the α -amino acids:

- 10 alanine,
- histidine,
- lysine,
- phenylalanine,
- proline,
- 15 tyrosine,
- valine,
- leucine,

- 104 -

- isoleucine,
 - glutamine,
 - methionine,
 - homoproline,
- 5 3-(2-thienyl) alanine, and
- 3-(3-thienyl) alanine.

The ICE inhibitors of another embodiment (F) of this invention are represented by formula δ :



10 wherein:

R_1 is $\text{R}_5-(\text{A})_{\text{p}}-$;

R_5 is selected from the group consisting of:

-H,

-Ar₁,

-CO-Ar₁,

-SO₂-Ar₁,

-R₉,

-CO-R₉,

-CO-O-R₉,

-SO₂-R₉,

/Ar₁

-CO-N
 \R₁₀,

/Ar₁

25 -SO₂-N
 \R₁₀,

/R₉

-CO-N
 \R₁₀, and

/R₉

30 -SO₂-N
 \R₁₀;

- 105 -

each A is independently selected from the group consisting of any α -amino acid;

p is 0, 1, 2, 3 or 4;

5 each R₉ is a C₁₋₆ straight or branched alkyl group optionally singly or multiply substituted by -OH, -F, or =O and optionally substituted with one Ar₁ group;

each R₁₀ is independently selected from the group consisting of -H or a C₁₋₆ straight or branched alkyl group;

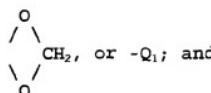
10 each T₁ is independently selected from the group consisting of:

-CH=CH-,
-O-,
-S-,
15 -SO-,

each Ar₁ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 20 15 carbon atoms and between 1 and 3 rings, said cycloalkyl group being optionally benzofused, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocycle group containing at least one heteroatom group selected from 25 -O-, -S-, -SO-, -SO₂-, -N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂, -CN, =O, -OH,
30

- 106 -

-perfluoro C₁₋₃ alkyl,

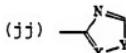


5

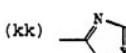
each Ar₂ is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by -Q₁ and -Q₂:

10 (ii)

;



; and



;

15

each Q₁ is independently selected from the group consisting of:

-Ar₁,

-O-Ar₁

20

-R₉,

-T₁-R₉, and

-(CH₂)_{1,2,3}-T₁-R₉;

25

each Q₂ is independently selected from the group consisting of -OH, -NH₂, -CO₂H, -Cl, -F, -Br, -I,

-NO₂, -CN, -CF₃, and



30

provided that when -Ar₁ is substituted with a Q₁ group which comprises one or more additional -Ar₁

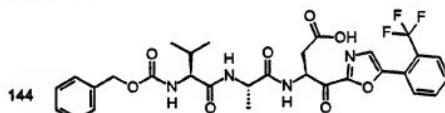
- 107 -

groups, said additional -Ar₁ groups are not substituted with Q₁:

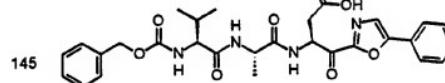
each X is independently selected from the group consisting of =N-, and =CH-; and

5 each Y is independently selected from the group consisting of -O-, -S-, and -NH.

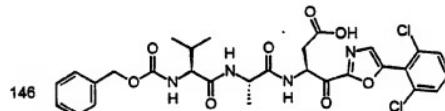
Preferred compounds of embodiment F of this invention include but are not limited to:



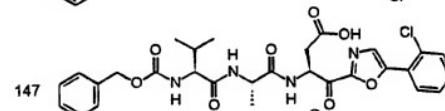
144 ;



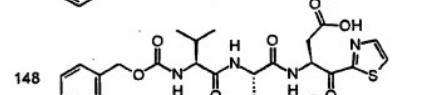
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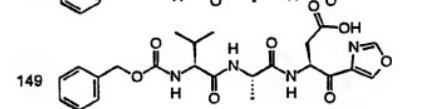


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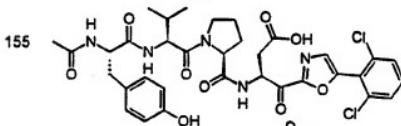
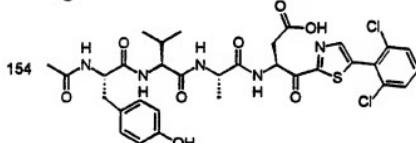
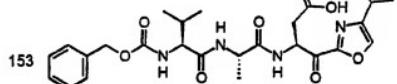
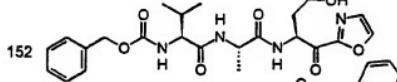
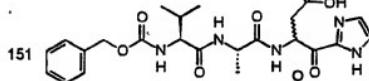
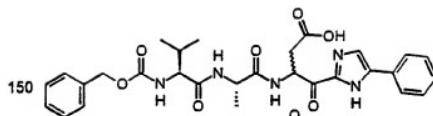
148 ;



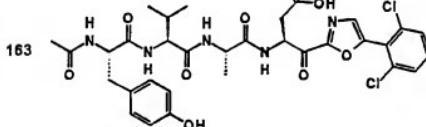
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149 ;

- 108 -



10



Preferred compounds of embodiment F of this invention are also those in which A is independently selected from the group consisting the α -amino acids:
alanine,

- 109 -

histidine,
lysine,
phenylalanine,
proline,
5 tyrosine,
valine,
leucine,
isoleucine,
glutamine,
10 methionine,
homoproline,
3-(2-thienyl) alanine, and
3-(3-thienyl) alanine.

The compounds of this invention having a
15 molecular weight of less than or equal to about 700
Daltons, and more preferably between about 400 and 600
Daltons, are preferred. These preferred compounds may
be readily absorbed by the bloodstream of patients upon
oral administration. This oral availability makes such
20 compounds excellent agents for orally-administered
treatment and prevention regimens against IL-1 mediated
diseases.

The ICE inhibitors of this invention may be
synthesized using conventional techniques.
25 Advantageously, these compounds are conveniently
synthesized from readily available starting materials.

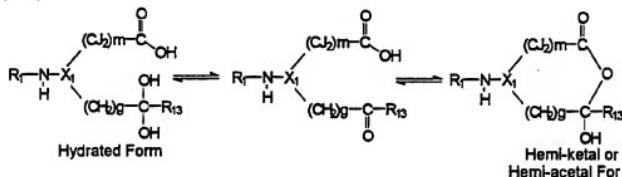
The compounds of this invention are among the
most readily synthesized ICE inhibitors known.
Previously described ICE inhibitors often contain four
30 or more chiral centers and numerous peptide linkages.
The relative ease with which the compounds of this
invention can be synthesized represents an enormous
advantage in the large scale production of these

- 110 -

compounds.

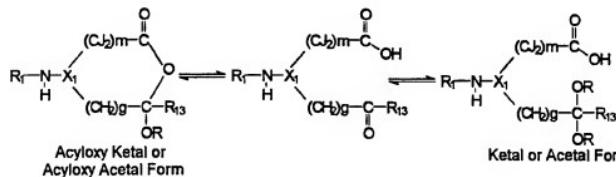
It should be understood that the compounds of this invention may exist in various equilibrium forms, depending on conditions including choice of solvent, pH, and others known to the practitioner skilled in the art. All such forms of these compounds are expressly included in the present invention. In particular, many of the compounds of this invention, especially those which contain aldehyde or ketone groups in R, and carboxylic acid groups in T, may take hemi-ketal (or hemi-acetal) or hydrated forms, as depicted below:

(EQ1)



Depending on the choice of solvent and other conditions known to the practitioner skilled in the art, compounds of this invention may also take acyloxy ketal, acyloxy acetal, ketal or acetal form:

(EQ2)



In addition, it should be understood that the equilibrium forms of the compounds of this invention may include tautomeric forms. All such forms of these

- 111 -

compounds are expressly included in the present invention.

It should be understood that the compounds of this invention may be modified by appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion. In addition, the compounds may be altered to pro-drug form such that the desired compound is created in the body of the patient as the result of the action of metabolic or other biochemical processes on the pro-drug. Some examples of pro-drug forms include ketal, acetal, oxime, and hydrazone forms of compounds which contain ketone or aldehyde groups, especially where they occur in the R₃ group of the compounds of this invention.

The compounds of this invention are excellent ligands for ICE. Accordingly, these compounds are capable of targeting and inhibiting events in IL-1 mediated diseases, such as the conversion of precursor IL-1 β to mature IL-1 β and, thus, the ultimate activity of that protein in inflammatory diseases, autoimmune diseases and neurodegenerative diseases. For example, the compounds of this invention inhibit the conversion of precursor IL-1 β to mature IL-1 β by inhibiting ICE. Because ICE is essential for the production of mature IL-1, inhibition of that enzyme effectively blocks initiation of IL-1 mediated physiological effects and symptoms, such as inflammation, by inhibiting the production of mature IL-1. Thus, by inhibiting IL-1 β precursor activity, the compounds of this invention

- 112 -

effectively function as IL-1 inhibitors.

The compounds of this invention may be employed in a conventional manner for the treatment of diseases which are mediated by IL-1. Such methods of treatment, their dosage levels and requirements may be selected by those of ordinary skill in the art from available methods and techniques. For example, a compound of this invention may be combined with a pharmaceutically acceptable adjuvant for administration to a patient suffering from an IL-1 mediated disease in a pharmaceutically acceptable manner and in an amount effective to lessen the severity of that disease.

Alternatively, the compounds of this invention may be used in compositions and methods for treating or protecting individuals against IL-1 mediated diseases over extended periods of time. The compounds may be employed in such compositions either alone or together with other compounds of this invention in a manner consistent with the conventional utilization of ICE inhibitors in pharmaceutical compositions. For example, a compound of this invention may be combined with pharmaceutically acceptable adjuvants conventionally employed in vaccines and administered in prophylactically effective amounts to protect individuals over an extended period time against IL-1 mediated diseases.

The compounds of this invention may also be co-administered with other ICE inhibitors to increase the effect of therapy or prophylaxis against various IL-1-mediated diseases.

In addition, the compounds of this invention may be used in combination either conventional anti-inflammatory agents or with matrix metalloprotease inhibitors, lipoxygenase inhibitors and antagonists of cytokines other than IL-1 β .

- 113 -

The compounds of this invention can also be administered in combination with immunomodulators (e.g., bropirimine, anti-human alpha interferon antibody, IL-2, GM-CSF, methionine enkephalin, 5 interferon alpha, diethyldithiocarbamate, tumor necrosis factor, naltrexone and rEPO) or with prostaglandins, to prevent or combat IL-1-mediated disease symptoms such as inflammation.

When the compounds of this invention are 10 administered in combination therapies with other agents, they may be administered sequentially or concurrently to the patient. Alternatively, pharmaceutical or prophylactic compositions according to this invention may be comprised of a combination of 15 an ICE inhibitor of this invention and another therapeutic or prophylactic agent.

Pharmaceutical compositions of this invention comprise any of the compounds of the present invention, and pharmaceutically acceptable salts thereof, with any 20 pharmaceutically acceptable carrier, adjuvant or vehicle. Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, 25 aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium 30 hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, 35 waxes, polyethylene-polyoxypropylene-block polymers,

- 114 -

polyethylene glycol and wool fat.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, 5 buccally, vaginally or via an implanted reservoir. We prefer oral administration. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. The term parenteral 10 as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

The pharmaceutical compositions may be in the 15 form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile 20 injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butandiol. Among the acceptable 25 vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be 30 employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in 35 their polyoxyethylated versions. These oil solutions

- 115 -

or suspensions may also contain a long-chain alcohol diluent or dispersant such as Ph. Egly or a similar alcohol.

5 The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, and aqueous suspensions and solutions. In the case of tablets for oral use, 10 carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous 15 suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

20 The pharmaceutical compositions of this invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the 25 rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

30 Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the pharmaceutical composition should be formulated with a suitable 35 ointment containing the active components suspended or

- 116 -

dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches are also included in this invention.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

The IL-1 mediated diseases which may be treated or prevented by the compounds of this invention include, but are not limited to, inflammatory diseases, autoimmune diseases and neurodegenerative diseases.

Inflammatory diseases which may be treated or prevented include, for example, septic shock, septicemia, and adult respiratory distress syndrome. Target autoimmune diseases include, for example, rheumatoid, arthritis, systemic lupus erythematosus,

- 117 -

scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis and multiple sclerosis. And target neurodegenerative diseases include, for example, amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, and primary lateral sclerosis. The ICE inhibitors of this invention may also be used to promote wound healing. And the ICE inhibitors of this invention may be used to treat infectious diseases.

Although this invention focuses on the use of the compounds disclosed herein for preventing and treating IL-1-mediated diseases, the compounds of this invention can also be used as inhibitory agents for other cysteine proteases.

The compounds of this invention are also useful as commercial reagents which effectively bind to ICE or other cysteine proteases. As commercial reagents, the compounds of this invention, and their derivatives, may be used to block proteolysis of a target peptide or may be derivatized to bind to a stable resin as a tethered substrate for affinity chromatography applications. These and other uses which characterize commercial cystine protease inhibitors will be evident to those of ordinary skill in the art.

In order that this invention be more fully understood, the following examples are set forth. These examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.

- 118 -

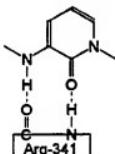
Example 1

The following example demonstrates a process of drug design which embodies the present invention:

Step 1) Pick 2 hydrogen bonding moieties of ICE,
5 here, the backbone C=O and N-H of Arg-341.

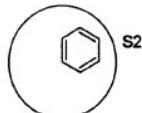
Step 2) Pick a scaffold, here, a pyridone derivative, and confirm that the hydrogen bonding moieties of the scaffold are capable of forming satisfactory hydrogen bonds with the hydrogen
10 bonding moieties selected in step 1. This confirmation is performed by using molecular mechanics techniques to minimize the scaffold fragment in the context of the active site of ICE.

(Z1)



Step 3) Pick a hydrophobic pocket, here, S2, as next target and a hydrophobic moiety, here, benzene. Minimize the benzene group within the S2 pocket to assure that substantial hydrophobic overlap is obtained.
15

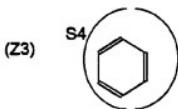
(Z2)

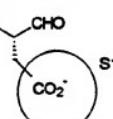


Step 4) Pick another hydrophobic pocket, here, S4, as the next target and a hydrophobic moiety,
20

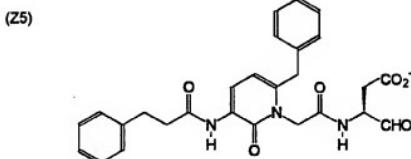
- 119 -

here, benzene. Minimize the benzene group within the S4 pocket to ensure that substantial hydrophobic overlap is obtained.



- 5 Step 5) Fill the S1 polar pocket with an electronegative moiety, here, a carboxylate sidechain provided by aspartic acid in which the C-terminus has been reduced to an aldehyde. Minimize to ensure that the carboxylate sidechain retains a favorable electrostatic interaction with the S1 polar pocket.
- 10 (Z4) 

- 15 Step 6) Link the scaffold with the moieties from steps 3, 4, and 5, preferably using the minimum number of bonds consistent with a chemically reasonable structure. Minimize the entire composite molecule in the active site of ICE.



- 120 -

Step 7) Evaluate the energy of the molecule when it has the conformation necessary for binding to ICE. Then minimize and reevaluate the energy -- this is the free conformation energy. The strain energy for binding of the potential inhibitor to ICE is the difference between the free conformation energy and the bound conformation energy. The strain energy should be less than about 10 kcal/mol. In this case the bound conformation energy is -1.6 kcal/mol and the free conformation energy is -11.7 kcal/mol, for a strain energy of 10.1 kcal/mol.

Step 8) The inhibitor designed using the above steps has been made and has been shown to have a K_i of 150 nM.

Example 2

We obtained inhibition constants (K_i) and IC_{50} values for several compounds of this invention using the three methods described below:

20 1. Enzyme assay with UV-visible substrate

This assay is run using an Succinyl-Tyr-Val-Ala-Asp-pNitroanilide substrate. Synthesis of analogous substrates is described by L. A. Reiter (Int. J. Peptide Protein Res. 43, 87-96 (1994)). The assay mixture contains:

65 μ l buffer (10mM Tris, 1 mM DTT, 0.1% CHAPS @pH 8.1)
10 μ l ICE (50 nM final concentration to give a rate of ~1mOD/min)
5 μ l DMSO/Inhibitor mixture
20 μ l 400 μ M Substrate (80 μ M final concentration)
100 μ l total reaction volume

The visible ICE assay is run in a 96-well microtiter plate. Buffer, ICE and DMSO (if inhibitor

- 121 -

is present) are added to the wells in the order listed. The components are left to incubate at room temperature for 15 minutes starting at the time that all components are present in all wells. The microtiter plate reader
5 is set to incubate at 37°C. After the 15 minute incubation, substrate is added directly to the wells and the reaction is monitored by following the release of the chromophore (pNA) at 405 - 603 nm at 37°C for 20 minutes. A linear fit of the data is performed and the
10 rate is calculated in mOD/min. DMSO is only present during experiments involving inhibitors, buffer is used to make up the volume to 100 µl in the other experiments.

2. Enzyme Assay with Fluorescent Substrate

15 This assay is run essentially according to Thornberry et al. (Nature 356: 768-774 (1992)), using substrate 12 referenced in that article. The substrate is: Acetyl-Tyr-Val-Ala-Asp-amino-4-methylcoumarin (AMC). The following components are mixed:

20 65 µl buffer(10mM Tris, 1mM DTT, 0.1% CHAPS @pH8.1)
10 µl ICE (2 - 10 nM final concentration)
5 µl DMSO/inhibitor solution
20 µl 150 µM Substrate (30 µM final)
100µl total reaction volume

25 The assay is run in a 96 well microtiter plate. Buffer and ICE are added to the wells. The components are left to incubate at 37°C for 15 minutes in a temperature-controlled wellplate. After the 15 minute incubation, the reaction is started by adding
30 substrate directly to the wells and the reaction is monitored @37°C for 30 minutes by following the release of the AMC fluorophore using an excitation wavelength for 380 nm and an emission wavelength of 460 nm. A linear fit of the data for each well is performed and a

- 122 -

rate is determined in fluorescence units per second.

For determination of enzyme inhibition constants (K_i) or the mode of inhibition (competitive, uncompetitive or noncompetitive), the rate data 5 determined in the enzyme assays at varying inhibitor concentrations are computer-fit to standard enzyme kinetic equations (see I. H. Segel, Enzyme Kinetics, Wiley-Interscience, 1975).

3. Cell assay

10 IL-1 β Assay with a Mixed Population of Human Peripheral Blood Mononuclear Cells (PBMC) or Enriched Adherent Mononuclear Cells

Processing of pre-IL-1 β by ICE can be measured in cell culture using a variety of cell 15 sources. Human PBMC obtained from healthy donors provides a mixed population of lymphocyte subtypes and mononuclear cells that produce a spectrum of interleukins and cytokines in response to many classes of physiological stimulators. Adherent mononuclear 20 cells from PBMC provides an enriched source of normal monocytes for selective studies of cytokine production by activated cells.

Experimental Procedure:

An initial dilution series of test compound 25 in DMSO or ethanol is prepared, with a subsequent dilution into RPMI-10% FBS media (containing 2 mM L-glutamine, 10 mM HEPES, 50 U and 50 ug/ml pen/strep) respectively to yield drugs at 4x the final test concentration containing 0.4% DMSO or 0.4% ethanol. 30 The final concentration of DMSO is 0.1% for all drug dilutions. A concentration titration which brackets the apparent K_i for a test compound determined in an ICE inhibition assay is generally used for the primary compound screen.

35 We generally test 5-6 compound dilutions and

- 123 -

have performed the cellular component of the assay in duplicate, with duplicate ELISA determinations on each cell culture supernatant.

PBMC Isolation and IL-1 Assay:

5 Buffy coat cells isolated from one pint human blood (yielding 40-45 ml final volume plasma plus cells) are diluted with media to 80 ml and LeukoPREP separation tubes (Becton Dickinson) are each overlaid with 10 ml of cell suspension. After 15 min
10 centrifugation at 1500-1800 xg, the plasma/media layer is aspirated and then the mononuclear cell layer is collected with a Pasteur pipette and transferred to a 15 ml conical centrifuge tube (Corning). Media is added to bring the volume to 15 ml, gently mix the
15 cells by inversion and centrifuge at 300 xg for 15 min. Resuspend the PBMC pellet in a small volume of media, count cells and adjust to 6×10^6 cells/ml.

For the cellular assay, add 1.0 ml of the cell suspension to each well of a 24-well flat bottom tissue culture plate (Corning), 0.5 ml test compound dilution and 0.5 ml LPS solution (Sigma #L-3012; 20 ng/ml solution prepared in complete RPMI media; final LPS concentration 5 ng/ml). The 0.5 ml additions of test compound and LPS are usually sufficient to mix the 20 contents of the wells. Three control mixtures are run per experiment, with either LPS alone, solvent vehicle control, and/or additional media to adjust the final culture volume to 2.0 ml. The cell cultures are
25 incubated for 16-18 hr at 37°C in the presence of 5% CO₂.

At the end of the incubation period, cells are harvested and transferred to 15 ml conical centrifuge tubes. After centrifugation for 10 min at 200 xg, supernatants are harvested and transferred to 35 1.5 ml Eppendorf tubes. It may be noted that the cell

- 124 -

pellet may be utilized for a biochemical evaluation of pre-IL-1 β and/or mature IL-1 β content in cytosol extracts by western blotting or ELISA with pre-IL-1 β specific antisera.

5 Isolation of Adherent Mononuclear cells:

PBMC are isolated and prepared as described above. Media (1.0 ml) is first added to wells followed by 0.5 ml of the PBMC suspension. After a one hour incubation, plates are gently shaken and nonadherent 10 cells aspirated from each well. Wells are then gently washed three times with 1.0 ml of media and final resuspended in 1.0 ml media. The enrichment for adherent cells generally yields $2.5\text{--}3.0 \times 10^5$ cells per well. The addition of test compounds, LPS, cell 15 incubation conditions and processing of supernatants proceeds as described above.

ELISA:

We have used Quantikine kits (R&D Systems) for measurement of mature IL-1 β . Assays are performed 20 according to the manufacturer's directions. Mature IL-1 β levels of about 1-3 ng/ml in both PBMC and adherent mononuclear cell positive controls are observed. ELISA assays are performed on 1:5, 1:10 and 1:20 dilutions of supernatants from LPS-positive 25 controls to select the optimal dilution for supernatants in the test panel.

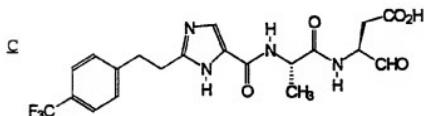
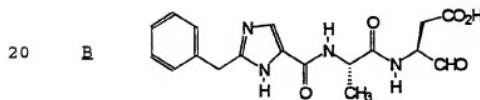
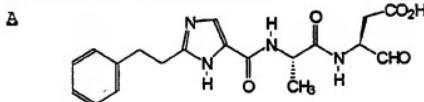
The inhibitory potency of the compounds can be represented by an IC₅₀ value, which is the concentration of inhibitor at which 50% of mature IL-1 β is detected in the supernatant as compared to the 30 positive controls.

The following K_i and IC₅₀ values were determined for compounds A through N using the indicated assays. Structures for compounds A through N follow this table.

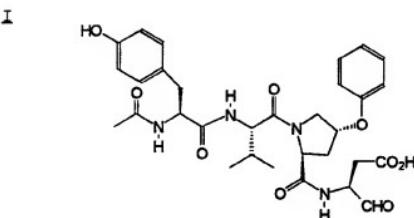
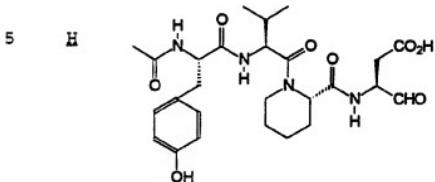
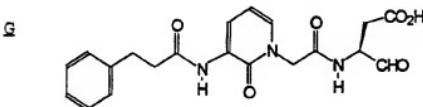
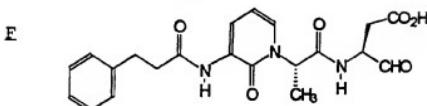
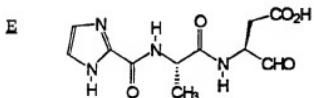
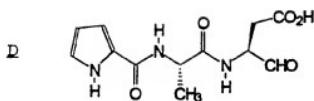
- 125 -

	<u>Compound</u>	<u>K_i (μM) by indicated assay:</u>		
		<u>UV-visible</u> K_i (μM)	<u>Fluorescence</u> K_i (μM)	<u>Cell</u> IC_{50} (μM)
5	A	5.5		25.0
	B	8.6		20.0
	C	10		>30
	D	4.7		
	E	3.2		
	F	0.15		2 - 4
10	G	4.8		
	H	0.023	0.0047	6 - 11
	I	0.0072	0.0052	2.6
	J	0.012	0.0039	5 - 7
	K	0.010	0.002	2 - 11
	L	0.014		
15	M	0.15		
	N	0.95		

Structures of compounds A through N:

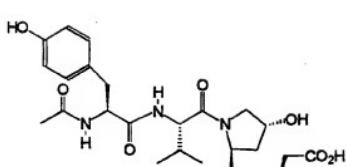


- 126 -

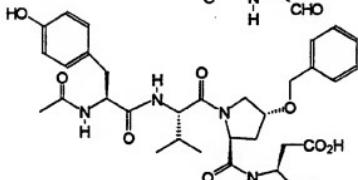


- 127 -

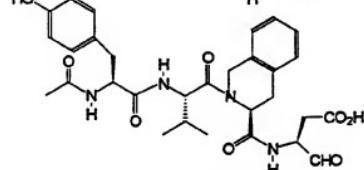
I



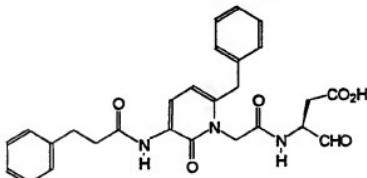
K



L

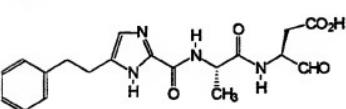


M



5

N



- 128 -

Example 3

Compounds of Example 2 were synthesized as follows:

5 H. N-(N-Acetyl-tyrosinyl-valinyl-pipecolyl)-3-amino-4-
oxobutanoic acid.

Step A. N-(N-tert-Butoxycarbonylpipecolyl)-4-
amino-5-benzyloxy-2-oxotetrahydrofuran.

10 Reaction of N-tert-butoxycarbonylpipecolic acid (460 mg, 2.0 mmol) and N-allyloxycarbonyl-4-amino-5-
benzyloxy-2-oxotetrahydrofuran (530 mg, 1.82 mmol) was carried out by a method analogous to that reported by Chapman (Bioorg. & Med. Chem. Lett. 1992, 2, 613-618.) to give 654 mg of the title compound.

15 ¹H NMR (500 MHz, CDCl₃, (existing as rotamers)) δ
7.35 (m, 5H), 6.88 (br. s, 1H), 4.9-4.45(m, 4H), 3.95
(br. m, 2H), 3.06 (m, 1H), 2.9 (m, 1H), 2.7 (br. m,
1H), 2.45 (m, 1H), 2.2 (m, 1H), 1.7-1.5 (m, 3H), 1.45
(two s, 9H).

20 Step B. N-Pipecolyl-4-amino-5-benzyloxy-2-
oxotetrahydrofuran.

25 N-(N-tert-Butoxycarbonylpipecolyl)-4-amino-5-benzyloxy-2-oxo-tetrahydrofuran (654 mg) was dissolved in 15 ml of 25% trifluoroacetic acid in dichloromethane and stirred at room temperature. The mixture was concentrated to give a gummy residue. The residue was dissolved in dichloromethane and washed with 10% sodium bicarbonate. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to give 422 mg of the title compound as a beige solid.

- 129 -

5 ¹H NMR (500 MHz, CDCl₃) δ 7.38 (m, 5H), 7.15 (d, 1H), 5.55 (d, 1H), 4.95-4.8 (m, 1H), 4.78 (m, 1H), 4.65 (d, 1H), 4.45 (m, 1H), 3.2 (m, 0.5H), 3.05 (m, 0.5H), 2.95 (m, 0.5H), 2.85 (m, 0.5H), 2.65 (m, 1H), 2.55-2.38 (m, 1H), 1.95 (m, 1H), 1.8 (m, 1H), 1.6 (m, 2H), 1.38 (m, 2H).

Step C. N-(N-Acetyl-tyrosinyl-valinyl-pipecolyl)-4-amino-5-benzyloxy-2-oxotetrahydrofuran.

10 N-Acetyl-tyrosinyl-valine (464 mg, 1.44 mmol) and N-Pipecolyl-4-amino-5-benzyloxy-2-oxotetrahydrofuran (412 mg, 1.3 mmol) were dissolved in 5 ml each of dimethylformamide and dichloromethane and cooled to 0°C. To the cooled solution was added 1-hydroxybenzotriazole (HOBT; 210 mg, 1.56 mmol) followed by the addition of 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC; 326 mg, 1.7 mmol). After stirring for 18 hours, the mixture was diluted with ethyl acetate and washed with water, 10% sodium hydrogen sulfate, 10% sodium bicarbonate, and water. The organic layer was concentrated to give a crude solid that was purified by flash chromatography (SiO₂) eluting with 94:6:1 (dichloromethane:isopropanol:pyridine) to give 370 mg of the title compound.

15 ¹H NMR (500 MHz, CD₃OD (existing as diastereomers as well as rotamers)) δ 7.35 (m, 5H), 7.05 (m, 2H), 6.68 (m, 2H), 5.65 & 5.25 (m, 1H), 4.9-3.95 (m, 8H), 3.4-2.6 (m, 4H), 2.5-2.1 (m, 1H), 1.98 (s, 1H), 1.9 (s, 1H), 1.85 (s, 1H), 1.8-1.6 (m, 2H), 1.55-1.3 (m, 4H), 0.95-0.85 (m, 6H).

- 130 -

Step D. N-(N-Acetyl-tyrosinyl-valinyl-pipecolyl)-3-amino-4-oxobutanoic acid.

To a solution of 100 mg of N-(N-Acetyl-tyrosinyl-valinyl-pipecolyl)-4-amino-5-benzyloxy-2-oxotetrahydrofuran in 10 ml of methanol was added 60 mg of Pd(OH)₂ on carbon and the mixture placed under an atmosphere of hydrogen via a balloon. The mixture was filtered through Celite and concentrated providing a white solid. This crude solid was dissolved in 2 ml of methanol and triturated with diethyl ether affording 26 mg of the title compound.

¹H NMR (500 MHz, CD₃OD (existing as diastereomers as well as rotamers)) δ 7.1 (m, 2H), 6.7 (m, 2H), 5.2 (br. m, 1H), 4.8-3.6 (m, 6H), 3.2-2.5 (m, 4H), 2.5-2.1 (m, 1H), 1.95 (three s, 3H), 1.9-1.3 (m, 6H), 1.1-0.7 (m, 6H).

The following compounds were prepared by a method analogous to that reported for H:

I. N-[N-Acetyl-tyrosinyl-valinyl-(4-hydroxyprolinyl)]-3-amino-4-oxobutanoic acid

Substitute N-tert-butoxycarbonyl-4-benzyloxyproline for N-tert-butoxycarbonylpiperolic acid.

L. N-[2-(N-Acetyl-tyrosinyl-valinyl)-(S)-1,2,3,4-tetrahydroisoquinoline-3-carbonyl]-3-amino-oxobutanoic acid

Substitute (S)-N-tert-butoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid for N-tert-butoxycarbonylpiperolic acid.

- 131 -

I. N-(N-Acetyl-tyrosinyl-valinyl-(4-phenoxyprolinyl))-3-amino-4-oxobutanoic acid.

Step A. N-tert-Butoxycarbonyl-4-phenoxyproline methyl ester.

To a cooled solution (0° C) of N-tert-butoxycis-4-hydroxyproline (2.0 g, 8.15 mmol), phenol (0.77 g, 8.15 mmol), and triphenylphosphine (2.14 g, 8.15 mmol) in 20 ml of tetrahydrofuran was added diethyl azodicarboxylate (1.4 ml, 9 mmol) dropwise over 30 minutes. The reaction was stirred at room temperature for 16 hrs. then concentrated to give a viscous residue. The crude residue was purified by flash chromatography (SiO₂) eluting with 3:7 (ethyl acetate:hexane) to give 1.89 g of the title compound.

¹H NMR (500 MHz, CDCl₃) δ 7.3 (m, 2H), 6.95 (m, 1H), 6.85 (d, 2H), 4.9 (m br., 1H), 4.55-4.15 (m, 2H), 3.88-3.65 (m, 1H), 3.70 (s, 3H), 2.58 (m, 1H), 2.22 (m, 1H), 1.4 (3 x s, 9H).

Step B. 4-Phenoxyproline methyl ester hydrochloride.

To a cooled solution (ice bath) of N-tert-Butoxycarbonyl-4-phenoxyproline methyl ester (0.6 g) in 20 ml of ethyl acetate was bubbled anhydrous hydrogen chloride until saturated. The mixture was warmed to room temperature and stirred for 3 hrs. then concentrated to give 480 mg of the title compound.

¹H NMR (500 MHz, CDCl₃) δ 7.22 (m, 2H), 6.95 (m 1 H), 6.83 (m, 2H), 5.1 (br., 1H), 4.6 (br. m, 1H), 4.06

- 132 -

(br. m, 1H), 3.75 (s, 3H), 3.55 (br. m, 1H), 2.58 (m, 2H).

Step C. N-Acetyl-tyrosinyl-valinyl-(4-phenoxy)proline methyl ester.

5 N-Acetyl-tyrosinyl-valine (0.524 g, 1.63 mmol) and 4-phenoxyproline methyl ester (0.381 g, 1.48 mmol) were dissolved in 4 ml each of dimethylformamide and dichloromethane and cooled to 0° C. To the cooled solution was added diisopropylethylamine (258 ul, 1.86 mmol), HOBT (0.24 g, 1.78 mmol), and EDC (0.37 g, 1.92 mmol) and the reaction was stirred for 18 hrs. The mixture was diluted with 400 ml of ethyl acetate and washed with water, 10% sodium hydrogen sulfate, 10% sodium bicarbonate, and water. The organic layer was concentrated to give a residue that was purified by flash chromatography (SiO_2) eluting with 94:6:1 (CH_2Cl_2 :i-PrOH:Pyridine) to afford 360 mg of the title compound.

20 ^1H NMR (500 MHz, CDCl_3 , (existing as rotamers)) δ 7.3 (m, 2H), 7.05 (m, 1H), 6.95 (d, 2H), 6.9-6.2 (4 x d, 4H), 5.05 (br. s, 1H), 4.7-3.94 (m, 5H), 2.93 (m, 1H), 2.82 (m, 1H), 2.65 (m, 1H), 2.2 (m, 1H), 2.05 (m, 1H), 1.95 (s, 3H), 1.86, (m, 1H), 0.98 (d, 3H), 0.88 (d, 3H).

25 Step D. N-Acetyl-tyrosinyl-valinyl-(4-phenoxy)proline.

30 Lithium hydroxide (57 mg, 1.37 mmol) was added to a solution of N-Acetyl-tyrosinyl-valinyl-(4-phenoxy)proline methyl ester (360 mg, 0.685 mmol) dissolved in 8 ml of tetrahydrofuran/water (1:1) and

- 133 -

stirred at room temperature for 1 hour. The mixture was acidified with 10% hydrochloric acid giving a white precipitate that was collected to give 175 mg of the title compound.

5 ¹H NMR (500 MHz, DMSO-d6) δ 9.2 (br. s, 1H),
8.05-7.95 (m, 2H), 7.3 (m, 1H), 7.0-6.9 (m, 4H), 6.65
(d, 2H), 4.42 (m, 1H), 4.35 (m, 1H), 4.05-3.95 (m, 2H),
3.3 (br. s, 2H), 2.75 (m, 1H), 2.55-2.38 (m, 2H), 2.2
(m, 1H), 2.0 (m, 1H), 1.7 (s, 3H), 0.95 (d, 3H), 0.85
10 (d, 3H).

Step E. N-[N-Acetyl-tyrosinyl-valinyl-(4-phenoxy)prolinyl]-4-amino-5-benzyloxy-2-oxotetrahydrofuran.

15 The title compound was prepared by the method reported for compound H, step A, by reaction of N-N-acetyl-tyrosinyl-valinyl-(4-phenoxy)proline and N-N-allyloxycarbonyl-4-amino-5-benzyloxytetrahydrofuran.

20 ¹H NMR (500 MHz, CDCl₃, (existing as a 1:1 diastereomer mixture of the hemiacetal)) δ 7.8-6.3 (m, 17H), 5.6 (d, 1H), 5.1-4.15 (m, 5H), 4.15-3.75 (m, 2H), 2.95-2.15 (m, 5H), 2.15-1.95 (m, 1H), 1.9-1.85 (2 x s, 3H), 1.1-0.75 (m, 6H).

25 Step F. N-[N-Acetyl-tyrosinyl-valinyl-(4-phenoxy)prolinyl]-3-amino-4-oxobutanoic acid.

The title compound was prepared by the hydrogenolysis procedure reported for compound H, step D.

- 134 -

¹H NMR (500 MHz, CD₃OD (existing as a 1:1 diastereomer mixture of the hemiacetal)) δ 7.25 (m, 2H), 7.10-6.85 (m, 5H), 6.65 (d, 2H), 5.1 (br. m, 1H), 4.65-4.05 (m, 5H), 4.0-3.40 (m, 2H), 2.95-2.35 (m, 5H), 5 2.25 (m, 1H), 2.05 (m, 1H), 1.85 (s, 3H), 1.0 (d, 3H), 0.95 (d, 3H).

K. N-[N-Acetyl-tyrosinyl-valinyl-(4-benzyloxy)prolinyl]-3-amino-4-oxobutanoic acid.

Step A. N-(N-Allyloxycarbonyl-4-benzyloxyprolinyl)-3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone.

The title compound was prepared by the reaction of N-allyloxycarbonyl-4-benzyloxyproline and 3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone (T.L. Graybill et. al., Abstracts of papers, 206th National Meeting of the American Chemical Society, Abstract MEDI-235. Chicago, IL. (1993)) under similar peptide coupling conditions as reported above (compound H; Step C).

20 ¹H NMR (500 MHz, CDCl₃) δ 9.05 (br. s, 1H), 7.85 (br. m, 1H), 7.4-7.2 (m, 5H), 7.15 (br. s, 1H), 6.55 (br. s, 1H), 5.9 (m, 1H), 5.1-4.9 (br. m, 2H), 4.65-4.4 (m, 4H), 4.2 (br. m, 1H), 3.75-3.5 (m, 2H), 2.75-2.55 (m, 2H), 2.5 (br. m, 1H), 2.25 (br. m, 1H) 1.4 (s, 9H).

25 Step B. N-(N-Acetyl-tyrosinyl-valinyl-(4-benzyloxyprolinyl)-3-amino-4oxobutanoic acid tert-butyl ester semicarbazone.

The title compound was prepared by reaction of N-acetyl-tyrosinyl-valine and N-(N-allyloxycarbonyl-4-

- 135 -

benzyloxyprolinyl)-3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone by reaction conditions reported for compound H, step A.

5 ¹H NMR (500MHz, CD₃OD) δ 7.35-7.2 (m, 6H), 7.0 (d, 2H), 6.65 (d, 2H), 4.85 (m, 1H), 4.6-4.45 (m, 4H), 4.3 (br. m, 1H), 4.15 (m, 1H), 3.7 (m, 1H), 2.95 (m, 1H), 2.75-2.6 (m, 3H), 2.35 (m, 1H), 2.1 (m, 1H), 1.9 (s, 3H), 1.4 (s, 9H), 0.95 (d, 3H), 0.90 (s, 3H).

10 Step C. N-(N-Acetyl-tyrosinyl-valinyl)-(4-benzyloxyprolinyl))-3-amino-4oxobutanoic acid.

15 N-(N-Acetyl-tyrosinyl-valinyl)-(4-benzyloxyprolinyl))-3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone (270 mg) was dissolved into 10 ml of 25% trifluoroacetic acid in dichloromethane and stirred at room temperature for 3 hours. The mixture was concentrated to give a solid residue. The residue was dissolved into a 10 ml mixture of methanol:acetic acid:37% formaldehyde (3:1:1) and 20 stirred at room temperature for 1 hour. The mixture was concentrated and the resulting residue purified by flash chromatography (SiO₂) eluting with dichloromethane/methanol/formic acid (100:5:0.5) to give 37 mg of the title compound.

25 ¹H NMR (500 MHz, CD₃OD (existing as a 1:1 mixture of diastereomers of the hemiacetal)) δ 7.4-7.25 (m, 5H), 7.0 (d, 2H), 6.65 (d, 2H), 4.65-4.05 (m, 7H), 3.75-3.4 (m, 2H), 3.05-2.3 (m, 5H), 2.2-1.95 (m, 2H), 1.90 (s, 3H), 1.0 (d, 3H), 0.95 (d, 3H).

- 136 -

Example 4

We obtained inhibition constants (K_i) and IC_{50} values for several compounds of this invention using enzyme assays with UV-visible substrate and cell assays
 5 as described in Example 2. The following K_i and IC_{50} values were determined for compounds 7a, 7b, 20a-d,
 21c-f, 22e, 25, 28, 33a-c, 36a, 36b, 39, 43, 47a, 47b,
 54a-l, 63, 69a, 69b, 84a and 84b using the indicated
 10 assays. Corresponding lettered compound designations
 structures are indicated parenthetically. The compound
 15 structures are shown in Examples 2 and 5.

		Assay	
		UV-visible	Cell
		K_i (μM)	IC_{50} (μM)
15	7a	35	
	7b	1.2	
	20a (= E)	3.2	
	20b	0.85	16.4
	20c (= N)	0.95	
	20d	0.1	6.2
20	21c	0.64	
	21d	0.24	4.8
	21e	0.22	2.9
	21f	0.17	2.9
	22e	0.19	
	25	6.2	
25	28	12.0	
	33a (= A)	5.5	25.0
	33b (= C)	10.0	>30.0
	33c (= B)	8.6	20.0
	36a (= D)	4.7	
	36b	0.8	17.0
30	39	2.5	
	43	20.0	

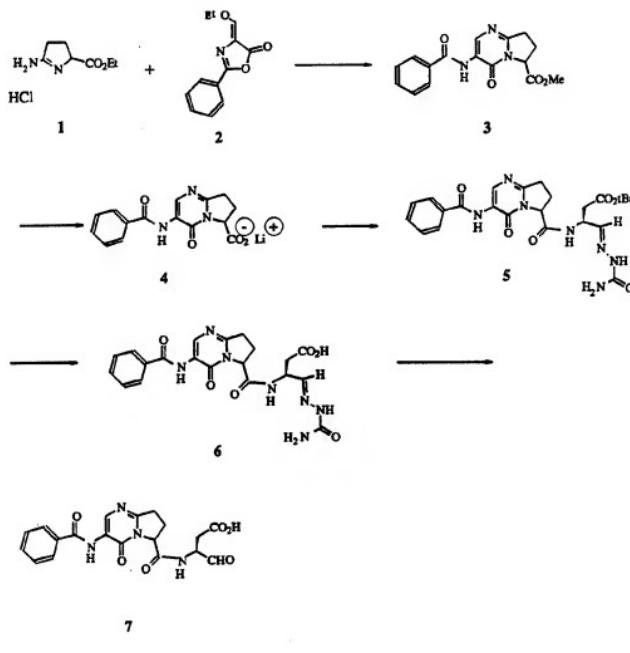
- 137 -

	47a	0.019	2.1
	47b	0.027	1.8
	54a (= E)	0.15	2.7
	54b (= M)	0.15	9.1
5	54c	1.2	>19.0
	54d	1.0	
	54e	3.5	
	54f	0.9	
	54g (= Q)	4.8	>20.0
10	54h	0.97	
	54i	0.054	2.4
	54j	0.28	
	54k	0.085	
	54l	0.215	7.0
15	63 (= Q)	0.85	4.1
	69a (= R)	0.011	0.735
	69b (= S)	0.050	0.745
	84a (= V)	0.100	3.3
	84b (= W)	0.019	0.50

- 138 -

Example 5

Compounds of Example 4 were synthesized as follows:



- 139 -

3-Benzoylamino-4-oxo-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-6-carboxylic acid methyl ester (3). A mixture of (4S)-2-amino-1-pyrroline-5-carboxylic acid ethyl ester hydrochloride (1, 0.44g, 2.38mmol; prepared in an analogous fashion as the methyl ester as described by Lee and Lown, *J. Org. Chem.*, 52, 5717-21 (1987)); 4-ethoxymethylene-2-phenyl-2-oxazolin-5-one (2, 0.50g, 2.31mmol) and sodium methoxide (0.12g, 2.22mmol) in ethanol (10ml) was refluxed for 2h. The reaction was allowed to cool to room temperature and concentrated in vacuo. The residue was suspended in water and 1N sulfuric acid was added until pH 1 was reached. The aqueous mixture was extracted with dichloromethane, the organic layer was separated and concentrated in vacuo to yield 0.6g of a orange solid. Chromatography (flash, SiO_2 , 60% ethyl acetate/hexane increased to 100% ethyl acetate stepwise gradient, then 10% methanol/dichloromethane) to give 0.5g of an orange solid. A mixture of the orange solid and potassium cyanide (0.03g, 0.5mmol) in methanol (10ml) was refluxed overnight. The cooled reaction was concentrated in vacuo to give a yellow solid. Chromatography (flash, SiO_2 , 40% ethyl acetate/hexane to 100% ethyl acetate stepwise gradient) afforded 0.22g (31.6%) of the title compound: ^1H NMR (d_6 -DMSO) δ 2.25 (m, 1H), 2.65 (m, 1H), 3.15 (m, 2H), 3.75 (s, 3H), 5.15 (dd, 1H), 7.5 (t, 2H), 7.6 (t, 1H), 7.95 (d, 2H), 8.6 (s, 1H), 9.5 (s, 1H).

(3S)-[(3-benzoylamino-4-oxo-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-6-carbonyl)-amino]-4-oxo-butanoic acid tert-butyl ester semicarbazone (5a and 5b). A mixture of 3-benzoylamino-4-oxo-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-6-carboxylic acid ethyl ester (3, 0.22g 0.70mmol) and lithium hydroxide

- 140 -

hydrate (0.032g, 0.76mmol) in methanol (5ml) and tetrahydrofuran (5ml) and was stirred 18h at room temperature. The reaction was concentrated to give 3-benzoylamino-4-oxo-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-6-carboxylic acid lithium salt (4) as a white solid. This was used without further purification in the subsequent reaction.

A 0°C mixture of (3S)-amino-4-oxo-butanoic acid tert-butyl ester semicarbazone (0.163g, 0.71mmol; Graybill et al., *Int. J. Protein Res.*, 44, pp. 173-82 (1994)) and 3-benzoylamino-4-oxo-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-6-carboxylic acid lithium salt (4) in dimethylformamide (5ml) and dichloromethane (5ml) was treated with hydroxybenzotriazole (0.104g, 0.77mmol) and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrogen chloride (0.148g, 0.37mmol). The reaction was allowed to warm to room temperature and stirred 18hr. The reaction was poured onto water (50ml) and extracted with ethyl acetate (2 x 50mL). The combined organic layers were washed with aqueous 1M sodium hydrogen sulfate solution, dilute aqueous sodium hydrogen carbonate (50mL) and saturated aqueous sodium chloride. The organic layer was concentrated in vacuo to yield 0.43g of a yellow solid. Chromatography (flash, SiO₂, ammonium hydroxide/methanol/di-chloromethane (1:1:99 to 1:10:90 stepwise gradient)) gave 0.11g (30.9%) of the higher R_f diastereomer (5a): ¹H NMR (CD₃OD) δ 1.45 (s, 9H), 2.29-2.35 (m, 1H), 2.6-2.7 (m, 2H), 2.8 (dd, 1H), 3.1-3.15 (m, 1H), 3.2-3.3 (m, 1H), 4.9-4.95 (m, 1H), 5.2 (dd, 1H), 7.25 (d, 1H), 7.5-7.55 (m, 2H), 7.55-7.6 (m, 1H), 7.95 (d, 2H), 8.9 (s, 1H) and 0.11g (30.9%) of the lower R_f diastereomer (5b): ¹H NMR (CD₃OD) δ 1.45 (s, 9H), 2.3-2.4 (m, 1H), 2.6-2.7 (m, 1H), 2.7-2.8 (m, 2H), 3.1-3.15 (m, 1H), 3.2-3.3 (m, 1H), 4.85-4.95 (m, 1H), 5.15 (dd, 1H), 7.25

- 141 -

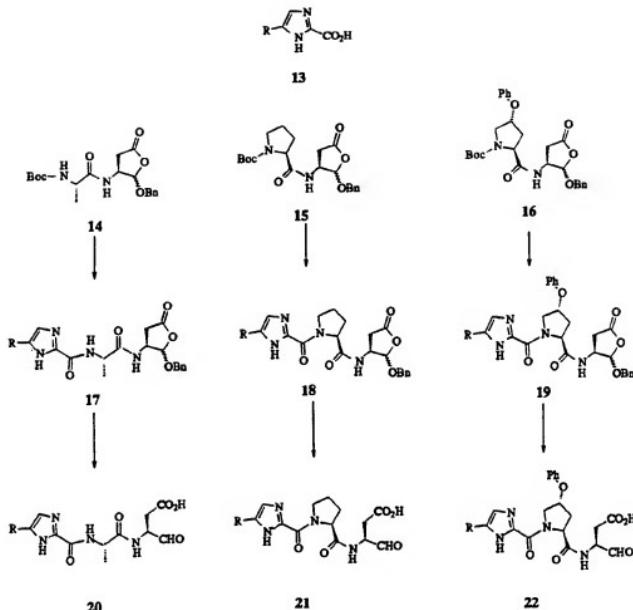
(d, 1H), 7.55 (t, 2H), 7.6 (t, 1H), 7.95 (d, 2H), 8.9 (s, 1H). Diastereomer 5a and diastereomer 5b were taken on separately.

5 (3S)-[(3-benzoylamino-4-oxo-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-6-carbonyl)-amino]-4-oxo-butanoic acid (7a). A suspension of (3S)-[(3-benzoylamino-4-oxo-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-6-carbonyl)-amino]-4-oxo-butanoic acid tert-butyl ester semicarbazone (5a, 0.11g, 0.22mmol) in
10 dichloromethane (7.5ml) and trifluoroacetic acid (2.5ml) was stirred for 5h. The reaction was concentrated in vacuo, the residue was taken up in dichloromethane, concentrated in vacuo, suspended in toluene and concentrated in vacuo to give 0.07 g of
15 (3S)-[(3-benzoylamino-4-oxo-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-6-carbonyl)-amino]-4-oxo-butanoic acid semicarbazone (6a) as a white solid. The solid was suspended in a mixture of 37% aqueous formaldehyde/acetic acid/methanol (1:1:5) and stirred
20 at room temperature for 18hr. The reaction was concentrated in vacuo, the residue was suspended in acetonitrile and concentrated in vacuo to give 0.1g of a white solid. Chromatography (HPLC, reverse phase C18, 1% to 75% acetonitrile/water (buffered with 0.1% trifluoroacetic acid) gradient elution) to give 0.05g
25 (60%) of 7a as a white solid: RT = 7.9 min (HPLC, C18 reverse phase, 1 to 100% acetonitrile/water (0.1% trifluoroacetic acid buffer); 20 min gradient elution);
30 ¹H NMR (CD₃OD (existing as a 1:1 mixture of anomers of the hemi-acyloxy acetal form)) δ 2.25-2.4 (m, 1H), 2.45-2.8 (m, 4H), 3.05-3.15 (m, 1H), 4.25-4.35 (m, 1H), 4.55-4.6 (m, 1H), 5.1-5.2 (m, 1H), 7.45-7.65 (m, 3H), 7.9-8.0 (m, 2H), 8.9 (s, 1H).

- 142 -

(3S)-[(3-benzoylamino-4-oxo-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-6-carbonyl)-amino]-4-oxo-butanoic acid (7b) was prepared as described for diastereomer 7a to give 0.03g (35%) of 7b as a white
5 solid: RT = 8.1 min (HPLC, C18 reverse phase, 1 to 100% acetonitrile/water (0.1% trifluoroacetic acid buffer); 20 min gradient elution); ¹H NMR (d_6 -DMSO
existing as a 1:1 mixture of anomers of the hemi-
acycloxy acetal form) δ 2.1-2.2 (m, 1H), 2.4 (d, 1H),
10 2.7-2.8 (m, 1H), 3.0-3.2 (m, 3H), 5.0 (dd, 1H), 5.1-5.2 (m, 1H), 5.5 (s, 1H), 5.7-5.8 (m, 1H), 7.55 (t, 2H), 7.67 (t, 1H), 7.95 (d, 2H), 8.55 (s, 1H), 9.0-9.15 (m, 1H), 9.4-9.5 (m, 1H).

- 143 -



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- | | |
|---|--|
| a | R = H |
| b | R = PhCH ₂ |
| c | R = Ph(CH ₂) ₂ |
| d | R = Ph(CH ₂) ₃ |
| e | R = 4MeO-Ph(CH ₂) ₃ |
| f | R = 4HO-Ph(CH ₂) ₃ |

10 Imidazole-2-carboxylic acids 13 were prepared using modifications of described procedures (Yamanaka et al., *Chem. Pharm. Bull.*, 31, pp. 4549-53 (1983)); Suzuki et al., *J. Org. Chem.*, 38, pp. 3571-75 (1973)); and Oliver et al. (*J. Org. Chem.*, 38, pp. 1437-38 (1973)).

- 144 -

Imidazole-2-carboxylic acid (13a) was prepared according to Curtis and Brown, *J. Org. Chem.*, 45, pp. 4038-40 (1980).

4-Benzylimidazole-2-carboxylic acid (13b), was isolated
5 as an off-white solid: mp. 153-155°C; IR (KBr) 3026-
2624, 1630, 1515, 1498, 1438, 1405; ¹H NMR(d₆-DMSO) δ
7.31 (5H, m), 7.14 (1H, s), 3.95 (2H, s).

4-(2-Phenylethyl)imidazole-2-carboxylic acid (13c), was isolated as a pale yellow solid: mp. 151-153°C; IR
10 (KBr) 3054-2617, 1637, 1497, 1376; ¹H NMR(d₆-DMSO) δ
7.27 (5H, m), 7.11 (1H, s), 2.92 (4H, s).

4-(3-Phenylpropyl)imidazole-2-carboxylic acid (13d), was isolated as a pale yellow solid: mp. 148-150°C; IR
15 (KBr) 3020-2615, 1636, 1509, 1498, 1383; ¹H NMR(d₆-
DMSO) δ 7.35-7.22 (5H, m), 7.01 (1H, s), 2.62 (4H, m),
1.94 (2H, m).

4-[3-(4-Methoxyphenyl)propyl]imidazole-2-carboxylic acid (13e), was isolated as a white crystalline solid:
mp. 155-156°C (decomp.); IR (KBr) 3300-2300, 1633,
20 1513, 1376, 1244; ¹H NMR(d₆-DMSO) δ 9.50-7.50 (2H, bs),
7.15 (1H, s), 7.11 (2H, d, J=8.5), 6.84 (2H, d, J=8.5),
3.71 (3H, s), 2.60-2.50 (4H, m), 1.86 (2H, m). Anal.
Calcd for C₁₄H₁₆N₂O₃: C, 64.60; H, 6.20; N, 10.76.
Found: C, 64.45; H, 6.21; N, 10.70.

25 4-[3-(4-Hydroxyphenyl)propyl]imidazole-2-carboxylic acid (13f). A solution of the ethyl ester of 13e
(1.15g, 4.0mmol) in dry dichloromethane (50ml) was treated with boron tribromide (16ml, 1.0M solution in
CH₂Cl₂, 16.0mmol) at 0°C. After 15min at 0°C, the

- 145 -

mixture was warmed to 25°C and stirred for 16h. The reaction mixture was cooled in an ice bath and quenched with a dropwise addition of water (20ml). The resulting mixture was briefly stirred at 25°C then 5 filtered. The filtrate was carefully neutralised by the addition of solid NaHCO₃ to afford 13f (700mg, 71%) as a white solid: m.p. 186-187°C (decomp.) (recrystallised from MeOH); IR (KBr) 3500-2400, 2935, 1640, 1516, 1396, 1232; ¹H NMR(d₆-DMSO) δ 9.83 (3H, bs), 7.16 (1H, s), 6.98 (2H, d, J=8.2), 6.66 (2H, d, J=8.2), 2.60-2.40 (4H, m), 1.84 (2H, m). Anal. Calcd for C₁₃H₁₄N₂O₃: C, 63.40; H, 5.73; N, 11.38. Found: C, 62.96; H, 5.70; N, 11.27.

(2R,S, 3S) N²-Tert-butoxycarbonyl-N-(tetrahydro-2-15 benzyl oxy-5-oxo-3-furanyl)-L-alaninamide (14). Tri-n-butyl tin hydride (4.0ml, 14.9mmol) was added dropwise to a solution of (2R,S, 3S) 3-(N-allyloxycarbonyl) amino-2-benzyl oxy-5-oxotetrahydrofuran (Chapman, Bioorg. Med. Chem. Lett., 2, pp. 613-18 (1992); (2.91g, 20 10mmol)), N-tert-butoxycarbonyl-L-alanine (2.08g, 11mmol) and bis(triphenylphosphine)palladium (II) chloride (150mg) in dichloromethane (75ml) until the colour of the solution turned dark orange. Hydroxybenzotriazole (2.70g, 20mmol) was added, and the 25 mixture cooled to 0°C. 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (2.30g, 12mmol) was added then the mixture was allowed to warm slowly to room temperature during 4h. The mixture was diluted with ethyl acetate (250ml) and washed with 1N hydrochloric acid (3 x 150ml), saturated aqueous sodium 30 bicarbonate (3 x 150ml) and brine (2 x 150ml), then dried (MgSO₄), filtered and concentrated. The crude product was purified by column chromatography (50-70% ethyl acetate/hexane) to afford 3.17g (84%) of a

- 146 -

mixture of diastereomers. Recrystallization (ethyl acetate-hexane) gave colorless crystals: mp. 132-145°C; IR (KBr) 3357, 3345, 1781, 1688, 1661, 1535, 1517, 1165; ¹H NMR (d₆-DMSO) δ 8.49 (d, J = 6.8), 8.23 (d, J = 7.4), 7.40 (5H, m), 7.01 (1H, m), 5.68 (d, J = 5.0), 4.75 (m), 4.31 (m), 3.97 (1H, m), 2.82 (m), 3.11 (m), 2.82 (m), 2.59 (m), 2.45 (m), 1.40 (9H, s), 1.20 (d, J = 7.2), 1.16 (d, J = 7.2). Anal. Calcd for C₁₉H₂₅N₂O₆: C, 60.31; H, 6.92; N, 7.40. Found C, 60.30; H, 6.91; N, 7.38.

(2R,S, 3S) tert-Butoxycarbonyl-N-(tetrahydro-2-benzylloxy-5-oxo-3-furanyl)-L-prolinamide (15), was prepared by the method described for 14 to afford 1.64g (81%) of a colorless glass. IR (KBr) 3317, 2978, 1797, 1697, 1670, 1546, 1400, 1366, 1164, 1121; ¹H NMR (CDCl₃) δ 7.68 (1H, brm), 7.35 (5H, m); 5.53 (d, J=5.2), 5.43 (s), 4.93-4.61 (m), 4.44 (m), 4.25 (brm), 3.39 (2H, brm), 3.10-2.81 (1H, m), 2.44 (1H, m), 2.32 (brm), 1.88 (brm), 1.67 (brm), 1.42 (9H, s).

(2R,S, 3S) N-(N-tert-Butoxycarbonyl-(4(R)-phenoxy-L-prolinyl)-3-amino-2-benzylloxy-5-oxotetrahydrofuran (16) was prepared by the method described for 14 to afford 530mg (84%) of a colorless amorphous solid: ¹H NMR (CDCl₃) δ 7.65 (1H, m), 7.4-7.2 (7 H, m), 6.95 (1H, m), 6.85 (1H, m), 5.55(1H, d), 4.95 (1H, d), 4.8-4.7 (1H, brm), 4.65 (1H, d), 4.55-4.45 (1H, brm), 4.4-4.3 (0.5H, brm), 3.95-3.85 (0.5H, brm), 3.75-3.58 (2H, m), 2.95-2.8 (1H, m), 2.7-2.55 (1H, m), 2.54-2.4 (1H, m), 2.35-2.2 (1H, m), 1.4 (9H,s).

(2R,S, 3S) N²-[4-(3-Phenylpropyl)imidazole-2-carbonyl]-N-(tetrahydro-2-benzylloxy-5-oxo-3-furanyl)-L-alaninamide (17d). Trifluoroacetic acid (7ml) was

- 147 -

added to a solution of (*2R,S, 3S*) *N*²-tert-butoxycarbonyl-*N*-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-*L*-alaninamide (14) (1.00g, 2.64mmol) in dichloromethane (7ml) at 0°C. The mixture was stirred at 0°C for 75 min. The mixture was concentrated, and the residue treated with diethyl ether then the ether was removed under vacuum. This procedure was repeated twice to yield a pale yellow glass. The solid was dissolved in DMF (20ml). Diisopropylethylamine (1.38ml, 7.92mmol) followed by 4-(3-phenylpropyl)imidazole-2-carboxylic acid (13d) (0.67g, 290mmol), 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (0.56g, 2.90mmol) and hydroxybenzotriazole (0.71g, 5.28mmol) were then added to this solution. The mixture was stirred at room temperature for 20h then poured into brine. The mixture was extracted with ethyl acetate (3 x 50ml). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (2 x 100ml) then brine (2 x 100ml), dried (MgSO₄), filtered and concentrated. The residue was purified by column chromatography (ethyl acetate) to afford 0.99g (76%) of 17d as a mixture of diastereomers: IR (KBr) 3293, 3064, 2937, 1793, 1650, 1530, 1451, 1446, 1119; ¹H NMR (CDCl₃) δ 7.96 (brm), 7.62 (brd), 7.36-7.10 (10H, m), 6.88 (s), 6.86 (s), 5.53 (d, J=5.2), 5.48 (s), 4.87-4.52 (4H, m), 3.11-2.38 (2H, m), 2.65 (4H, m), 1.99 (2H, m), 1.47 (d, J=6.9), 1.46 (d, J=7.0).

The following compounds were prepared in a similar manner:

(*2R,S, 3S*) *N*²-(Imidazole-2-carbonyl)-*N*-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-*L*-alaninamide (17a), was

- 148 -

isolated (74%) as a pale yellow solid: IR (KBr) 3289,
3056, 2937, 1793, 1664, 1642, 1528, 1453, 1440, 1124;
¹H NMR (d₆-DMSO) δ 13.13 (1H, brs), 8.67 (d, J=7.0),
8.48 (d, J=7.8), 8.29 (d, J=6.8), 8.25 (d, J=7.6),
5 7.40-7.34 (6H, m), 7.11 (1H, s), 5.69 (d, J=5.0), 5.49
(d, J=0.8), 4.85-4.31 (4H, m), 3.19-2.42 (2H, m), 1.38
(d, J=7.4), 1.34 (d, J=7.4).

10 (2R,S, 3S) N²-(4-Benzylimidazole-2-carbonyl)-N-
(tetrahydro-2-benzylxy-5-oxo-3-furanyl)-L-alaninamide
15 (17b), was isolated (75%) as a pale yellow glass: IR
(KBr) 3294, 3031, 2937, 1792, 1650, 1530, 1453, 1444,
1119; ¹H NMR (CDCl₃) δ 7.99 (brm), 7.75 (brd), 7.36-7.11
(10H, m), 6.81 (1H, s), 5.51, 5.45 (d, s, J=5.3), 4.85-
4.47 (4H, m), 3.95 (2H, s), 3.04-2.72 (1H, m), 2.48-
2.35 (1H, m), 1.44 (d, J=6.9), 1.43 (d, J=7.1).

20 (2R,S, 3S) N²-[4-(2-Phenylethyl)imidazole-2-carbonyl]-N-
(tetrahydro-2-benzylxy-5-oxo-3-furanyl)-L-alaninamide
25 (17c), was isolated (79%) as a pale yellow glass: IR
(KBr) 3292, 3029, 2936, 1793, 1650, 1530, 1453, 1444,
1119; ¹H NMR (CDCl₃) δ 8.06 (brm), 7.70 (brs), 7.39-7.15
(10H, m), 6.82 (s), 6.81 (s), 5.53 (d, J=5.2), 5.48
(s), 4.87-4.53 (4H, m), 2.95 (4H, m), 3.11-2.37 (2H,
m), 1.48 (d, J=5.6), 1.45 (d, J=6.7).

30 (2R,S, 3S) 1-[4-(2-Phenylethyl)imidazole-2-carbonyl]-N-
(tetrahydro-2-benzylxy-5-oxo-3-furanyl)-L-prolinamide
(18c), was isolated (79%) as a pale yellow glass: IR
(CH₂Cl₂) 3422, 2959, 1795, 1685, 1611, 1497, 1116;
¹H NMR (d₆-DMSO) δ 12.78-12.59 (1H, m), 8.61-8.34 (1H,
m), 7.39-7.22 (10H, m), 6.99-6.61 (1H, m), 5.71-5.26
(1H, m), 4.85-4.02 (4H, m), 3.63 (1H, m), 3.18-1.74
(11H, m).

- 149 -

(2R,S, 3S) 1-[4-(3-Phenylpropyl)imidazole-2-carbonyl]-N-(tetrahydro-2-benzyl-oxy-5-oxo-3-furanyl)-L-prolinamide (18d), was isolated (87%) as a colorless glass: IR (CH₂Cl₂) 3422, 3214, 2945, 1794, 1685, 1604, 1496, 1117; ¹H NMR(d₆-DMSO) δ 12.71 (1H, brm), 8.61-8.34 (1H, m), 7.45-7.18 (10H, m), 7.05-6.64 (1H, m), 5.70-5.28 (1H, m), 4.85-4.02 (4H, m), 3.62 (1H, m) 3.18-1.71 (13H, m).

(2R,S, 3S) 1-[4-[3-(4-Methoxyphenyl)propyl]imidazole-2-carbonyl]-N-(tetra-hydro-2-benzylloxy-5-oxo-3-furanyl)-L-prolinamide (18e), was isolated (72%) as a white glassy solid: mp. 62-65°C; IR (KBr) 3213, 2937, 1793, 1680, 1606, 1606, 1512, 1245; ¹H NMR(d₆-DMSO) δ 12.71, 12.67, 12.58 (1H, 3 x bs), 8.60-8.30 (1H, m), 7.40-7.20 (5H, m), 7.15-6.55 (5H, m), 5.66-5.20 (1H, m), 4.81-4.59 (2H, m), 4.55-4.05 (2H, m), 3.71 (3H, s), 3.65-3.45 (1H, m), 3.15-1.50 (13H, m). FABMS m/e 547 (M⁺, 100%), 439, 412, 340, 312, 243, 177, 154.

(2R,S, 3S) 1-[4-[3-(4-Hydroxyphenyl)propyl]imidazole-2-carbonyl]-N-(tetra-hydro-2-benzylloxy-5-oxo-3-furanyl)-L-prolinamide (18f), was isolated (70%) as a light yellow glassy solid: mp. 86-90°C; IR (KBr) 3298, 1790, 1669, 1606, 1515, 1242; ¹H NMR(d₆-DMSO) δ 12.66, 12.56 (1H, 2 x bs), 9.14 (1H, s), 8.57-8.30 (1H, m), 7.36-7.30 (5H, m), 7.02-6.83 (3H, m), 6.70-6.57 (2H, m), 5.65-5.28 (1H, m), 4.80-4.49 (2H, m), 4.50-4.05 (2H, m), 3.65-3.45 (1H, m), 3.15-1.55 (13H, m). FABMS m/e 533 (M⁺, 100%), 425, 298, 229, 176, 154.

1-[5-[3-(4-Methoxyphenyl)propyl]-1H-imidazole-2-carbonyl]-4(R)-phenoxypprolidine-2(S)-carbonyl-(tetrahydro-2(R,S)-benzylloxy-5-oxofuran-3(S)-yl)amide (19e) was isolated (77%) as a clear colorless amorphous

- 150 -

solid. ^1H NMR (CDCl_3) δ 9.95-9.75 (1H, m), 7.95 (1H, brs), 7.40-7.2 (7H, m), 7.2-6.78 (7H, m), 5.65-5.6 (1H, m), 5.55-5.45 (1H, m), 5.3-5.2 (1H, m), 5.15-5.0 (1H, m), 4.95-4.75 (1H, m), 4.7-4.6 (1H, m), 4.5-4.4 (1H, m), 4.35-4.4.25 (1H, m), 3.8 (3H, s), 3.05-1.75 (10H, m).

(3S) 3-[N-[4-(3-Phenylpropyl)imidazole-2-carbonyl]-L-alaninyl]amino-4-oxo-butanoic acid (20d). A mixture of (2R,S, 3S) N^2 -[4-(3-Phenylpropyl)imidazole-2-carbonyl]-N-(tetrahydro-2-benzoyloxy-5-oxo-3-furanyl)-L-alaninamide (0.93g, 1.90mmol) and 10% palladium on activated carbon (0.93g) in methanol (100ml) was stirred under a hydrogen atmosphere for 5h. The resulting mixture was filtered and concentrated to yield a colorless glass. Recrystallization from methanol-diethyl ether afforded 401mg (53%) of 20d as a colorless solid: mp. 94-96°C; $[\alpha]_D^{27} +16.4^\circ$ (c 0.5, MeOH); IR (KBr) 3300, 3287, 1786, 1732, 1659, 1651, 1532, 1451; ^1H NMR (CD_3OD) δ 7.19 (5H, m), 6.91 (1H, s), 4.60-4.46 (2H, m), 4.27 (1H, m), 2.63 (4H, m), 2.75-2.40 (2H, m), 1.96 (2H, m), 1.44 (3H, d, $J=7.0$).

The following compounds were prepared in a similar manner:

(3S) 3-[N-(Imidazole-2-carbonyl)-L-alaninyl]amino-4-oxobutanoic acid (20a; E), was isolated (83%) as a colorless solid: mp. 115°C; $[\alpha]_D^{25} +4.4^\circ$ (c 0.5, MeOH); IR (KBr) 3303, 1782, 1658, 1650, 1563, 1521, 1454; ^1H NMR (CD_3OD) δ 7.18 (2H, s), 4.55 (2H, m), 4.27 (1H, m), 2.56 (2H, m), 1.45 (d, $J=7.1$), 1.44 (d, $J=7.0$).

(3S) 3-[N-(4-Benzylimidazole-2-carbonyl)-L-alaninyl]amino-4-oxobutanoic acid (20b), was isolated (56%) as a colorless solid: mp. 113-115°C; $[\alpha]_D^{29} +18.2^\circ$

- 151 -

(c 0.5 MeOH). IR (KBr) 3301, 3288, 1783, 1727, 1650, 1531, 1452; ^1H NMR (CD_3OD) δ 7.25 (5H, m), 6.90 (1H, s), 4.59-4.45 (2H, m), 4.26 (1H, m), 3.95 (2H, s), 2.74-2.39 (2H, m), 1.42 (3H, d, $J=7.0$). Anal. Calcd for $\text{C}_{18}\text{H}_{20}\text{O}_5$: C, 56.69; H, 5.55; N, 14.69. Found: C, 57.06; H, 5.54; N, 14.41.

(3S)-3-[N-[4-(2-Phenylethyl)imidazole-2-carbonyl]-L-alaninyl]amino-4-oxobutanoic acid (20c; N), was isolated (53%) as a colorless solid: mp. 102-104°C; $[\alpha]_D^{27} +13.7^\circ$ (c 0.5, MeOH); IR (KBr) 3299, 3289, 1785, 1732, 1650, 1531, 1452; ^1H NMR (CD_3OD) δ 7.20 (5H, m), 6.82 (1H, s), 4.60-4.46 (2H, m), 4.29 (1H, m), 2.92 (4H, s), 2.76-2.41 (2H, m), 1.44 (3H, 2 x d, $J=7.1$). Anal. Calcd for $\text{C}_{18}\text{H}_{22}\text{N}_4\text{O}_5\text{H}_2\text{O}$: C, 56.43; H, 5.98; N, 13.85. Found: C, 56.65; H, 5.84; N, 13.91.

(3S) 3-{N-[4-(2-Phenylethyl)imidazole-2-carbonyl]-L-prolinyl}amino-4-oxobutanoic acid (21c), was isolated (85%) as a colorless glass: mp. 101-103°C (methanol-diethyl ether); $[\alpha]_D^{27}$ -63.8° (c 0.25, MeOH); IR (KBr) 20 3275, 1784, 1728, 1664, 1606, 1498, 1429; ^1H NMR (CD₃OD) δ 7.24 (5H, m), 6.83 (s), 6.79 (s), 4.58-4.14 (3H, m), 3.69 (1H, m), 2.93 (4H, brs), 2.75-1.99 (6H, m). Anal. Calcd for C₂₁H₂₄N₄O₅ H₂O: C, 58.60; H, 6.09; N, 13.02. Found: C, 58.34; H, 5.96; N, 12.67.

25 (3S) 3-[N-[4-(3-Phenylpropyl)imidazole-2-carbonyl]-L-
prolinyl]amino-4-oxo-butanoic acid (21d), was
isolated(81%) as a colorless glass: mp. 91-94°C;
(methanol-diethyl ether); $[\alpha]_D^{25} -68^\circ$ (c 0.25, MeOH); IR
(KBr) 3277, 2939, 1784, 1727, 1662, 1606, 1498, 1429;
30 ^1H NMR (CD_3OD) δ 7.29-7.16 (5H, m), 6.92 (s), 6.86 (s),
4.58-4.16 (3H, m), 3.71 (1H, m), 2.75-1.92 (13H, m).
Anal. Calcd for $\text{C}_{22}\text{H}_{26}\text{NO}_5 \text{H}_2\text{O}$: C, 59.45; H, 6.35; N,

- 152 -

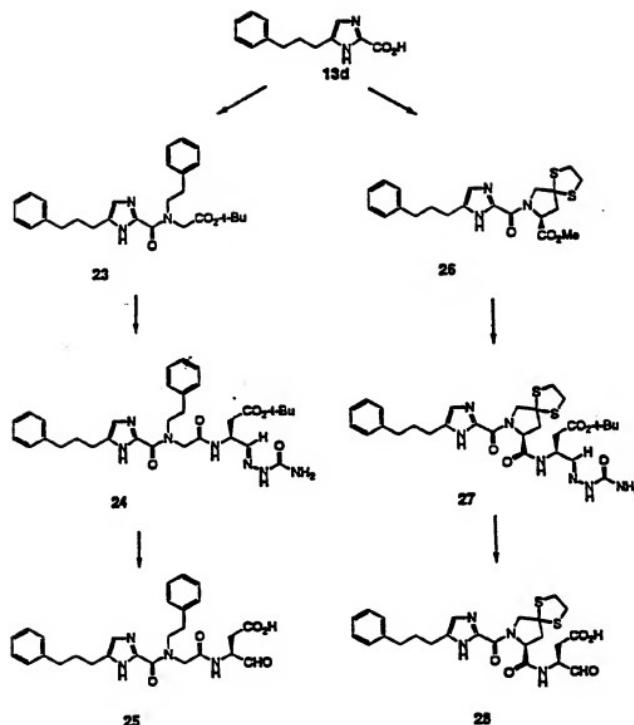
12.60. Found: C, 59.75; H, 6.21; N, 12.41.

(3*S*) 3-{N-[4-[3-(4-Methoxyphenyl)propyl]imidazole-2-carbonyl]-L-prolinyl}amino-4-oxobutanoic acid (21e), was isolated (65%) as a white glassy solid: mp. 101-
5 105°C; $[\alpha]_D^{23}$ -60.6 (c 0.05, MeOH); IR (KBr) 3231, 1784, 1726, 1611, 1512, 1245; ^1H NMR (CD₃OD) δ 7.09 (2H, d, J=8.6), 6.92, 6.85 (1H, 2 × s), 6.81 (2H, d, J=8.6), 5.45-5.30 (1H, m), 4.64-4.46 (1H, m), 4.28-4.10 (2H, m), 3.75 (3H, s), 3.74-3.66 (1H, m), 2.67-1.84 (13H, m). Anal. Calcd for C₂₃H₂₈N₄O₆ H₂O: C, 58.22; H, 6.37; N, 11.81. Found: C, 58.39; H, 6.34; N, 11.45; FABMS m/e 457 (M⁺), 405, 312, 243, 215, 176, 154 (100%).

(3*S*) 3-{N-[4-[3-(4-Hydroxyphenyl)propyl]imidazole-2-carbonyl]-L-prolinyl}amino-4-oxobutanoic acid (21f), was isolated (43%) as a white glassy solid: mp. 114-
15 118°C; $[\alpha]_D^{25}$ -55.7° (c 0.05, MeOH); IR (KBr) 3288, 2935, 1780, 1715, 1662, 1610, 1515, 1441; ^1H NMR (CD₃OD) δ 6.99 (2H, d, J=8.5), 6.91, 6.85 (1H, 2 × s), 6.68 (2H, d, J=8.5), 5.45-5.30 (1H, m), 4.60-4.47 (1H, m), 4.30-4.10 (2H, m), 3.80-3.55 (1H, m), 2.70-1.80 (13H, m). Anal. Calcd for C₂₂H₂₆N₄O₆ H₂O: C, 57.38; H, 6.13; N, 12.17. Found: C, 57.68; H, 6.25; N, 11.66. FABMS m/e 443 (M⁺), 298, 229, 154 (100%).

3(S)-[(1-{5-[3-(4-Methoxyphenyl)propyl]-1*H*-imidazole-2-carbonyl}-4(R)-phenoxy pyrrolidine-2(S)-carbonyl)amino]-4-oxobutanoic acid (22e) was isolated (43%) as a beige solid: ^1H NMR (CD₃OD) δ 7.35-7.2 (3H, m), 7.15-7.0 (2H, m), 6.98-6.85 (3H, m), 6.83-6.77 (2H, d), 5.4-5.1 (1H, m), 4.65-4.5 (1H, m), 4.35-4.2 (2H, m), 4.15-3.90 (1H, m), 3.78 (3H, s), 3.62-3.48 (1H, m), 2.78-2.25 (8H, m), 2.02-1.9 (2H, m).

- 153 -



- 154 -

{Phenethyl-[5-(3-propyl)-1H-imidazole-2-carbonyl]amino}acetic acid tert-butyl ester (23).

A 0°C solution of 4-(3-phenylpropyl)-imidazole-2-carboxylic (13d) (150mg, 0.65mmol) and N-(2-phenethyl)glycine tert-butyl ester (140 mg, 0.59 mmol) in 5 ml of anhydrous dimethylformamide was treated with diisopropylethylamine (154 μ l, 0.89mmol), hydroxybenzotriazole (160 mg, 1.18 mmol), and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (136 mg, 0.71 mmol). After stirring for 36 h, the reaction was poured onto saturated aqueous sodium chloride and extracted with ethyl acetate (3 x 50ml). The combined organic extracts were washed twice with saturated aqueous sodium bicarbonate (2x) and saturated aqueous sodium chloride (1x), dried (Na_2SO_4), filtered, and concentrated in vacuo to give a brown oil. Chromatography (flash, SiO_2 , 30% ethyl acetate/hexane) to give 160mg (61%) of 23 as a white solid: ^1H NMR (CDCl_3) δ 7.38-7.14 (10H, m), 6.85-6.8 (1H, m), 4.84-4.76 (1H, d), 4.5-4.42 (1H, m), 4.07-4.0 (1H, d), 3.78-3.72 (1H, m), 3.12-2.94 (2H, 2 x m), 2.75-2.55 (4H, m), 2.1-1.95 (2H,m), 1.5-1.45 (9H, 3 x s).

(3S)-[2-Phenethyl-[5-(3-phenylpropyl)-1H-imidazole-2-carbonyl]amino]acetyl amino 4-oxobutanoic acid tert-butyl ester semicarbazone (24). The ester 23 (160mg, 0.357mmol) was treated with 25% trifluoroacetic acid/dichloromethane (7ml) for 4 h. The reaction was concentrated in vacuo to afford 180mg of the acid. The acid (180 mg, 0.357mmol) was coupled to (3S)-3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone (161mg, 0.357mmol) as describe for the preparation of 5a and 5b to give 86 mg (33%) of 24 (one diastereomer) as a white solid : ^1H NMR (CDCl_3) δ 10.9-10.3 (1H, 2 d), 10.08-9.78 (1H, 2 d), 9.25-9.15 (1H,m), 8.35-8.10 (1H, 2 m),

- 155 -

7.9-7.85 (1H, 2 s), 7.40-7.05 (10H, m), 6.9-6.75 (1H,m), 6.3-5.8 (1H, br s), 5.2-4.65 (2H,m), 4.35-3.5 (3H,m), 3.25-3.0 (2H, m), 2.9-2.45 (6H,m), 2.05-1.8 (2H,m), 1.4 (9H,s).

5 (3S)-{2-[Phenethyl-[5-(3-phenylpropyl)-1H-imidazole-2-carbonyl]amino}acetyl amino}-4-oxobutanoic acid trifluoroacetic acid salt (25) was prepared by the method described for 7a to afford 32 mg (82%) as a white solid: ¹H NMR (CD₃OD) δ 7.05-7.35 (m, 11H), 4.65 (m, 1H), 4.4 (m, 1H), 4.3 (s, 2H), 3.6-4.0 (m, 2H), 2.5-2.95 (m, 8H), 2.05 (m, 2H).

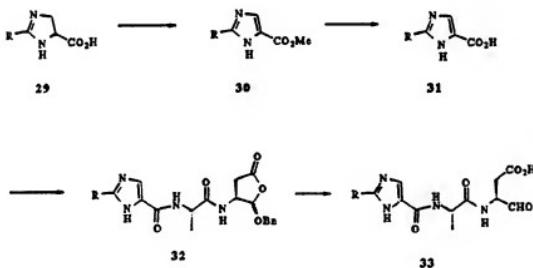
10 7-[5-(3-Phenylpropyl)-1H-imidazole-2-carbonyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid methyl ester (26). 4-(3-Phenylpropyl)imidazole-2-carboxylic acid (13d) was coupled to 1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid methyl ester hydrobromide (Smith et. al., *J. Med. Chem.*, 31, pp. 875-85 (1988)) by the method described for 23 to afford 140 mg (65%) as a yellow gum: ¹H NMR (CDCl₃) δ 7.34-7.15 (5H, m), 6.98-6.8 (1H, 3 s), 5.7-5.65 (0.5 H, m), 5.2-5.1 (1H,m), 4.82-4.75 (0.5H, m), 4.4-4.35 (1H, m), 4.05 (1H,d), 3.75-3.7 (3H, 2 s), 3.4-3.3 (4H,m), 2.95-2.45 (8H, m), 2.05-1.95 (2H,m).

15 (3S)-{[7-[5-(3-Phenylpropyl)-1H-imidazole-2-carbonyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carbonyl]-amino}-4-oxobutanoic acid tert-butyl ester semicarbazone (27). Following the procedure described for 4, the ester 26 was converted to its acid which was subsequently coupled to (3S)-3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone as described for 24 to give 70 mg (33%) as a brown solid : ¹H NMR (CD₃OD) δ 7.28-7.10 (5H,m), 6.90 (1H, br s), 4.94 (1H, m), 3.96-3.86

- 156 -

(2H, q), 3.35-3.25 (4H, d), 3.0 (2H, s), 2.73-2.59 (6H, m), 2.0-1.92 (2H, m), 1.44 (9H, s).

(3S)-{(7-[5-(3-Phenylpropyl)-1H-imidazole-2-carbonyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carbonyl)-amino}-4-oxobutanoic acid (28) was prepared by the method described for 7a to afford 17 mg (26%) as a light brown solid: ^1H NMR (CD_3OD) δ 7.4 (s, 1H), 7.1-7.25 (m, 5H), 4.9 (m, 1H), 4.6 (m, 1H), 4.3 (m, 1H), 3.95 (s, 2H), 3.25-3.4 (m, 4H), 3.0 (d, 2H), 2.6-2.8 (m, 5H), 2.45 (m, 1H), 2.05 (m, 2H).



a R = Ph(CH₂)₂
 b R = 4CF₃-Ph(CH₂)₂
 c R = PhCH₂

15

4,5-Dihydroimidazole-4-carboxylic esters (29) were prepared by a modification of the procedure described by Jones et al., Tetrahedron Lett., 29, pp. 3853-56 (1988).

(4*R,S*) Methyl 2-(2-phenylethyl)-4,5-dihydroimidazole-4-carboxylate (29a). Dry hydrogen chloride was bubbled

- 157 -

into a solution of hydrocinnamonnitrile (3.28ml, 25mmol) in methanol (125ml) at 0°C for 45 mins. The solvents were removed to give the imidate salt which was dissolved in methanol (125ml) along with methyl 2,3-diaminopropionate (25mmol) (Jones et al., supra). The mixture was kept at room temperature for 2.5h, then concentrated to a yellow oil. The crude product was purified by column chromatography (10-20% methanol/dichloromethane) to afford 3.52g (61%) of a colorless glass: ^1H NMR(CDCl₃) δ 7.30-7.15 (5H, m), 4.63 (1H, t, J=9.7), 3.96 (2H, d, J=9.7), 3.72 (3H, s), 3.10 (4H, m), ^{13}C NMR(CDCl₃) δ 171.3, 168.8, 138.3, 128.4, 128.2, 126.6, 57.3, 53.0, 47.7, 31.7, 27.9.

(4R,S) Methyl 2-[2-(4-trifluoromethylphenyl)ethyl]-4,5-dihydroimidazole-4-carboxylate (29b), was prepared by the method described for 29a to yield 6.80g (78%) of a colorless solid: mp. 136-141°C; ^1H NMR(CDCl₃) δ 7.45 (4H, s), 4.71 (1H, dd, J=8.6, 10.8), 4.02 (2H, m), 3.73 (3H, s), 3.19 (4H, m).

Imidazole-4-carboxylic esters 30 were prepared by a modification of the procedure described by Martin et al., J. Org. Chem., 33, pp. 3758-61 (1968).

Methyl 2-(2-phenylethyl)imidazole-4-carboxylate (30a). A mixture of (4R,S) methyl 2-(2-phenylethyl)-4,5-dihydroimidazole-4-carboxylate (29a) (3.40g, 14.64mmol), chloroform (75ml) and manganese (IV) oxide (13.0g, 150mmol) was heated under reflux for 21h then filtered hot. The solids were washed with chloroform and methanol. The combined filtrates were concentrated to leave a yellow-brown solid, which was purified by column chromatography (2-5% methanol/dichloromethane) to afford 1.46g (43%) of a pale yellow solid: mp. 151-

- 158 -

155°C; IR (KBr) 3028, 2946, 1720, 1533, 1433, 1348,
1195, 1166; ¹H NMR (CDCl₃) δ 7.62 (1H, s), 7.26-7.02 (5H,
m), 3.82 (3H, s), 3.03 (4H, brs), ¹³C NMR (CDCl₃) δ
162.9, 150.2, 140.3, 128.5, 128.2, 126.3, 51.5, 34.5,
5 30.4. Anal. Calcd for C₁₃H₁₄N₂O₂ : C, 67.81; H, 6.13; N,
12.16. Found: C, 67.70; H, 6.15; N, 12.16.

Methyl 2-[2-(4-trifluoromethylphenyl)ethyl]imidazole-4-carboxylate (30b), was prepared by the method described for 30a. It was recrystallised from ethyl acetate to afford 1.88g (33%) of cream crystals: mp. 225-26°C; IR (KBr) 3239, 2951, 1715, 1532, 1331, 1158, 1105, 1068; ¹H NMR (CDCl₃) δ 7.61 (1H, s), 7.54 (2H, d, J = 8.1), 7.26 (2H, d, J = 8.1), 3.89 (3H, s), 3.10 (4H, m).
Anal. Calcd for C₁₄H₁₃F₃N₂O₂: C, 56.38; H, 4.39; N, 9.39;
15 F, 19.11. Found: C, 56.23; H, 4.44; N, 9.33; F, 19.08.

2-(2-Phenylethyl)imidazole-4-carboxylic acid (31a). A mixture of methyl 2-(2-phenylethyl)imidazole-4-carboxylate (31a) (1.38g, 6mmol), methanol (30ml) and 1M aqueous sodium hydroxide (30ml) was heated under reflux for 16h. The methanol was removed under reduced pressure, and the resulting aqueous solution was neutralized with 4M hydrochloric acid, whereupon a pale yellow solid precipitated. The precipitate was collected, washed with water, and dried to afford 1.18g (91%) of a pale yellow solid: mp. 117-120°C; IR (KBr) 3375, 3131, 2616, 2472, 1638, 1592, 1551, 1421, 1388, 1360; ¹H NMR (d₆-DMSO) δ 7.59 (1H, s), 7.26 (5H, m), 2.99 (4H, m). Anal. Calcd for C₁₂H₁₂N₂O₂ 0.25H₂O: C, 65.29; H, 5.71; N, 12.69. Found: C, 65.00; H, 5.64; N, 12.58.

30 2-[2-(4-Trifluoromethylphenyl)ethyl]imidazole-4-carboxylic acid (31b), was prepared by the method described for 31a to afford 1.09g (76%) of a pale

- 159 -

yellow solid: mp. 126-130°C; IR (KBr) 3339, 2640-2467, 1638, 1589, 1545, 1383, 1323; ¹H NMR(d₆-DMSO) δ 7.69 (2H, d, J=8.0), 7.59 (1H, s), 7.47 (2H, d, J=8.0), 3.06 (4H, m).

5 (2R,S, 3S) N²-[2-(2-Phenylethyl)imidazole-4-carbonyl]-N-(tetrahydro-2-benzyl-oxy-5-oxo-3-furanyl)-L-alaninamide (32a). To a solution of (2R,S, 3S) N²-tert-butoxycarbonyl-N-(tetrahydro-2-benzylxy-5-oxo-3-furanyl)-L-alaninamide (14) (1.59g, 4.20mmol; Chapman,
10 Biorg. Med. Chem. Lett., 2, pp. 613-18 (1992)) in dichloromethane (15ml), cooled to 0°C, was added trifluoroacetic acid (15ml). The mixture was stirred at 0°C for 1h and then concentrated. The residue was treated with ether and then the ether was removed under vacuum. This procedure was repeated twice to yield a pale yellow glass. The solid was dissolved in DMF (20ml), then diisopropylethylamine (2.19ml, 12.6mmol), 2-(2-phenylethyl)imidazole-4-carboxylic acid (31a) (1.0g, 4.62mmol), 1-(3-dimethylaminopropyl)-3-ethyl
15 carbodiimide hydrochloride (0.89g, 4.62mmol) and hydroxybenzotriazole (1.14g, 8.40mmol) were added to the solution. The reaction mixture was stirred at room temperature for 20h then poured into brine. The mixture was extracted with ethyl acetate (3 x 50ml).
20 The combined organic extracts were washed with saturated aqueous sodium bicarbonate (3 x 100ml) then brine (3 x 100ml), dried (MgSO₄) and concentrated. The residue was purified by column chromatography (2-10% isopropanol in dichloromethane then 0-6% isopropanol in ethyl acetate) to yield 1.10g (55%) of 32a as a mixture of diastereomers: IR (KBr) 3278, 3065, 1790, 1641, 1577, 1545, 1499, 1454, 1120; ¹H NMR(CDCl₃) δ 10.26 (1H, s), 8.14 (1H, s), 7.66 (d, J=7.0), 7.56 (d, J=7.0), 7.43 (1H, s), 7.31-7.11 (10H, m), 5.49 (d, J=5.6), 5.48

- 160 -

(s), 4.83-4.41 (4H, m), 3.04-2.41 (2H, m), 2.99 (4H, s), 1.45 (d, J=7.0), 1.44 (d, J=7.0).

5 (2R,S, 3S) N²-{2-[2-(4-Trifluoromethylphenyl)ethyl]imidazole-4-carbonyl}-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-alaninamide (32b), was prepared by the method described for 32a to afford 1.08g (62%) of a pale yellow glass: IR (KBr) 3376, 3284, 3070, 2938, 1791, 1642, 1578, 1546, 1327, 1165, 1122, 1068; ¹H NMR (CDCl₃) δ 7.95 (0.5H, m), 7.55-7.25 (11.5H, m), 5.53 (s), 5.49 (d, J=5.3), 4.88-4.48 (4H, m), 3.11-2.96 (4H, m), 2.91 (1H, m), 2.51 (1H, m), 1.47 (3H, d, J=7.1).

10 (2R,S, 3S) N²-{(2-Benzylimidazole-4-carbonyl)-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-alaninamide (32c), was prepared by the method described for 32a from 2-benzylimidazole-4-carboxylic acid (Ger. Offen. DE 3427136) to afford 1.13g (83%) of a yellow glass: IR (CH₂Cl₂) 3433, 3062, 2990, 1803, 1693, 1584, 1504, 1429, 1285, 1258; ¹H NMR (CDCl₃) δ 9.50 (s), 9.37 (s), 7.86 (0.5H, d, J=6.1), 7.56-7.21 (10.5H, m), 7.48 (1H, s), 5.51 (d, J=5.2), 5.48 (s), 4.87-4.41 (4H, m), 4.08 (s), 4.07 (s), 3.03-2.39 (2H, m), 1.46 (3H, d, J=7.0).

15 (3S) 3-[N-[2-(2-Phenylethyl)imidazole-4-carbonyl]-L-alaninyl]amino-4-oxobutanoic acid (33a; A). A mixture of (2R,S, 3S) N²-[2-(2-phenylethyl)imidazole-4-carbonyl]-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-alaninamide (32a) (1.0g, 2.10mmol) and 10% palladium on activated carbon (1.0g) in methanol (50ml) was stirred under a hydrogen atmosphere for 4.5h. The resulting mixture was filtered and concentrated to yield a colorless glass. Recrystallization from methanol-diethyl ether afforded 510mg (63%) of a colorless

- 161 -

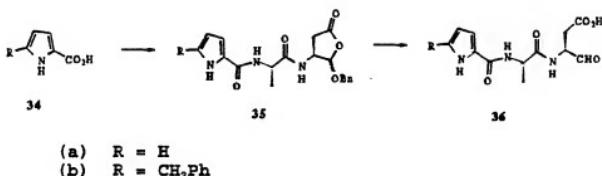
solid: mp. 127°C; IR (KBr) 3360, 3279, 2981, 1781, 1732, 1646, 1577, 1547; ¹H NMR (CD₃OD) δ 7.54 (1H, s), 7.29-7.12 (5H, m), 4.60-4.47 (2H, m), 4.28 (1H, m), 3.01 (4H, s), 2.76-2.39 (2H, m), 1.43 (3H, 2 x d, J=7.0, J=7.0), ¹³C NMR (CD₃OD) δ 176.2, 176.0, 174.7, 174.6, 164.4, 164.3, 150.5, 141.9, 134.8, 129.5, 129.3, 127.3, 122.3, 98.8, 98.4, 52.3, 52.0, 50.3, 35.6, 31.2, 18.8, 18.7. Anal. Calcd for C₁₈H₂₂N₄O₅ H₂O: C, 56.43; H, 5.98; N, 13.85. Found: C, 56.78; H, 5.70; N, 13.77.

(3S)-3-[N-[2-(2-[4-Trifluoromethylphenyl]ethyl)imidazole-4-carbonyl]-L-alaninyl]-amino-4-oxobutanoic acid (33b; G), was prepared by the method described for 33a to afford 612mg (73%) of a colorless solid: mp. 120-124°C; [α]_D²³ +14.3° (c 0.5, MeOH); IR (KBr) 3287, 2985, 2937, 1782, 1732, 1646, 1579, 1547, 1327; ¹H NMR (CD₃OD) δ 7.56 (2H, d, J=8.0), 7.54 (1H, s), 7.36 (2H, d, J=8.0), 4.60-4.48 (2H, m), 4.28 (1H, m), 3.08 (4H, m), 2.75-2.41 (2H, m), 1.43 (3H, d, J=7.0). Anal. Calcd for C₂₀H₂₁F₃N₄O₅. 0.5H₂O : C, 51.84; H, 4.78; N, 12.09; F, 12.30. Found: C, 51.83; H, 4.72; N, 12.14; F, 12.36.

(3S)-3-[N-(2-Benzylimidazole-4-carbonyl)-L-alaninyl]amino-4-oxobutanoic acid (33c; B), was prepared by the method described for 33a to afford 426mg (64%) of a colorless solid: [α]_D²³ +13.4° (c 0.407, MeOH). IR (KBr) 3260, 3150, 2980, 1779, 1727, 1649, 1573, 1547; ¹H NMR (CD₃OD) δ 7.58 (1H, s), 7.34-7.22 (5H, m), 4.59-4.47 (2H, m), 4.28 (1H, m), 4.07 (2H, s), 2.74-2.41 (2H, m), 1.42 (3H, d, J=6.7); ¹³C NMR (CD₃OD) δ 175.6, 175.5, 175.0, 164.6, 164.5, 150.1, 138.7, 135.3, 130.0, 129.9, 128.2, 122.9, 98.9, 98.5, 52.5, 52.2, 35.5, 35.1, 35.0, 19.0, 18.9. Anal. Calcd for C₁₈H₂₀N₄O₅ H₂O: C, 55.37; H, 5.68; N, 14.35. Found C,

- 162 -

55.83; H, 5.75; N, 13.96. MS(FAB, m/z) : 373 ((M⁺), 228, 185, 91.



- 5 5-Benzylpyrrole-2-carboxylic acid (34b). A mixture of Ethyl 5-benzylpyrrole-2-carboxylate (0.7g, 3.05mmol; Elder et al., *Synthetic Communications*, 19, 763-767 (1989)), ethanol (20ml) and 1M sodium hydroxide (9.2ml, 9.2mmol) was stirred and heated under reflux for 3h.
- 10 The major part of the ethanol was removed and the remaining liquid was diluted with water, washed with ether, cooled in ice and acidified with concentrated hydrochloric acid. The mixture was extracted with ether. The combined extracts were washed with brine, dried (Na₂SO₄) and concentrated to afford 0.567g (92%) of an off white solid: mp. 130-134°C; ¹H NMR(CDCl₃) δ 8.87 (1H, brs), 7.37-6.95 (5H, m), 6.97 (1H, m), 6.07 (1H, m), 4.00 (2H, s).
- 15 (2R,S, 3S) N²-(Pyrrole-2-carbonyl)-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-alaninamide (35a). A solution of (2R,S, 3S) N²-tert-butoxycarbonyl-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-alaninamide (14) (756mg, 2.0mmol) in dry dichloromethane (8ml) at 0°C was treated with trifluoroacetic acid (8ml) for 1h and then evaporated to dryness. Dry ether was added to the residue and the mixture concentrated to give a viscous oil. The oil was dissolved in dry DMF (10ml).

- 163 -

Pyrrole-2-carboxylic acid (34a) (244mg, 2.2mmol) was added and the solution was cooled in an ice bath before the addition of N,N-diisopropylamine (0.78g, 6.0mmol), 1-hydroxybenzotriazole (0.54g, 4.0mmol) and ethyl 5 dimethylaminopropyl carbodiimide hydrochloride (0.42g, 2.2mmol). The resulting mixture was stirred at 25°C for 17h and then saturated aqueous sodium chloride (30ml) was added. The mixture was extracted with ethyl acetate (3 x 20ml) and the combined organic extracts were washed with 5% aqueous sodium bicarbonate (3 x 10ml) and brine (10ml), dried (MgSO_4) and concentrated. 10 Flash chromatography (25% hexane-ethyl acetate) afforded 557mg (75%) of a 1:1 mixture of diastereomers as a white glassy solid: mp. 85-90°C; IR (KBr) 3288, 1789, 1665, 1629, 1557 and 1122; ^1H NMR (d_6 -DMSO) δ 11.46 (1H, bs), 8.55 (0.5H, d, $J=7.0$), 8.30 (0.5H, d, $J=7.6$), 8.06 (0.5H, d, $J=7.0$), 8.04 (0.5H, d, $J=7.6$), 7.36-7.30 (5H, m), 6.88-6.85 (2H, m), 6.10-6.07 (1H, m), 5.63 (0.5H, d, $J=5.0$), 5.42 (0.5H, s), 4.72 (2H, q, $J=12.2$), 15 4.74-4.25 (2H, m), 3.14-2.35 (2H, m), 1.29, 1.25 (3H, 20 2 x d, $J=7.2$).

(2R,S, 3S) N^2 -(5-Benzylpyrrole-2-carbonyl)-N-(tetrahydro-2-benzylxy-5-oxo-3-furanyl)-L-alaninamide (35b), was prepared from 5-benzylpyrrole-2-carboxylic acid (34b) by the method described for compound 35a (65%). Data is given for a single diastereomer. ^1H NMR (d_6 -DMSO) δ 11.37 (1H, brs,), 8.27 (1H, d, $J=7.4$), 7.93 (1H, d, $J=7.6$), 7.33-7.16 (10H, m), 6.76 (1H, m), 5.82 (1H, m), 5.62 (1H, d, $J=5.2$), 4.76 (1H, d, $J=12.0$), 25 4.65 (1H, m), 4.62 (1H, d, $J=12.2$), 4.47 (1H, m), 3.88 (2H, s), 2.77 (1H, dd, $J=9.0, 18.0$), 2.5 (dd), 1.23 (3H, d, $J=7.0$).

- 164 -

(3S) 3-[N-(Pyrrole-2-carbonyl)-L-alaninyl]amino-4-oxobutanoic acid (36a; D). A mixture of (35a) (612mg; 1.65mmol), methanol (40ml) and 10% palladium on carbon (500mg) was vigorously stirred under an atmosphere of hydrogen for 4h. The mixture was filtered through a 0.2 μ M nylon membrane then concentrated. The residue was purified by flash chromatography (5-10% methanol in methylene chloride) to afford the hemihydrate of (36a) (223mg, 48%) as a white solid after precipitation from an ethyl acetate-ether mixture. There were traces of solvent in the product: mp. 96-100°C; IR (KBr) 3381, 1774, 1729 (EtOAc), 1632, 1558, 1523, 1123; ¹H NMR (CD₃OD) δ 6.94-6.85 (2H, m), 6.17 (1H, dd, J=3.8 and 2.6), 4.58 (0.5H, d, J=3.94), 4.56 (0.5H, d, J=4.24), 4.51 (1H, q, J=7.16), 4.35-4.20 (1H, m), 2.74-2.40 (2H, m), 1.42 and 1.41 (3H, 2 x d, J=7.13).

(3S) 3-[N-(5-Benzylpyrrole-2-carbonyl)-L-alaninyl]amino-4-oxobutanoic acid (36b), was prepared (41%) from 35b by the method described for compound 36a, to afford an off white solid: mp. 109-112°C; [α]_D²⁵ +6.3° (c 0.3, methanol); IR (KBr) 3368, 1724, 1630, 1530, 1453, 1414, 1233, 1049; ¹H NMR (d₄ methanol) δ 7.25-7.11 (5H, m), 6.76 (1H, d, J=3.5), 5.84 (1H, d, J=3.5), 4.51 (1H, m), 4.43 (1H, q, J=7.1), 4.23 (1H, m), 2.5 (2H, m), 1.35 (3H, d, J=7.0). Anal. Calcd for C₁₉H₂₁N₃O₅ · 1.75 H₂O: C, 56.64; H, 6.13; N, 10.43. Found: C, 56.34; H, 5.72; N, 10.00.



38

39

- 165 -

(2R,S, 3S) 1-(Indole-2-carbonyl)-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-prolinamide (38).

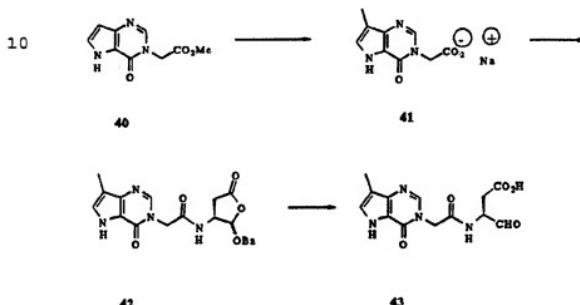
Trifluoroacetic acid (4ml) was added to a solution of

(2R,S, 3S) 1-tert-butoxycarbonyl-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-prolinamide (15) (0.607g, 1.5mmol) in dichloromethane (4ml) at 0°C. The mixture was stirred at 0°C for 75 min. The mixture was concentrated, and the residue treated with diethyl ether, then the ether was removed under vacuum. This procedure was repeated twice to yield a yellow oil, which was dissolved in DMF (12ml). Diisopropyl-ethylamine (0.78ml, 4.5mmol) followed by indole-2-carboxylic acid (266mg, 1.65mmol), 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (316mg, 1.65mmol) and hydroxybenzotriazole (405mg, 3mmol) were then added to the solution. The mixture was stirred at room temperature for 20h then poured into brine. The mixture was extracted with ethyl acetate (3 x 30ml). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (2 x 60ml) then brine (2 x 60ml), dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (ethyl acetate) to afford 518mg (77%) of a mixture of diastereomers: IR (KBr) 3314, 1780, 1677, 1609, 1524, 1435, 1406, 1344; 1H NMR (d_6 -DMSO), δ 11.58 (1H, m), 8.81-8.41 (1H, m), 7.71-6.67 (10H, m), 5.70 (d, $J=5.2$), 5.48 (s), 4.89-4.29 (4H, m), 3.99-3.74 (2H, m), 3.20-2.44 (2H, m), 2.39-1.77 (4H, m).

(3S) 3-[1-(Indole-2-carbonyl)-L-prolinyl]amino-4-oxobutanoic acid (39). A mixture of (2R,S, 3S) 1-(indole-2-carbonyl)-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-prolinamide (38) (478mg, 1.07mmol) and 10% palladium on carbon (475mg) and methanol (150ml) was stirred under a hydrogen atmosphere for 6h. The

- 166 -

resulting mixture was filtered and concentrated to yield a colorless glass. Recrystallization from a mixture of methanol and diethyl ether afforded 202mg (53%) of a colorless solid: mp. 135-138°C; $[\alpha]_D^{24} -44^\circ$ (c 5 0.25, CH₃OH); IR (KBr) 3287, 2977, 2879, 1781, 1725, 1716, 1667, 1662, 1600, 1529, 1441, 1346; ¹H NMR (CD₃OD) δ 7.65 (1H, d, J=8.0), 7.44 (1H, d, J=8.4), 7.22 (1H, m), 7.09-6.84 (2H, m), 4.62 (2H, m), 4.29 (1H, m), 4.15-3.73 (2H, m), 2.74-1.72 (6H, m).



Methyl 2-(3,5-dihydro-7-methyl-4-oxo-4H-pyrrolo [3,2-d] pyrimidin-3-yl)acetate (40). Freshly prepared methyl glycinate (1.25g, 14mmol) was added to a stirred solution of ethyl 3-[N-(dimethylamino) methylene]amino-15 4-methylpyrrole-2-carboxylate (1.56g, 7.0mmol; Lim et al., J. Org. Chem., 44, pp. 3826-29 (1979)) in dry methanol (60ml). The resulting mixture was kept at 70°C. Two further batches of methyl glycinate (1.25, 20 14.0mmol) were added after 18h and 42h heating. The mixture was cooled and filtered 24h after the final addition. The filtrate was concentrated and the residue purified by flash chromatography (2-5%

- 167 -

methanol/chloroform) to afford 0.54g (35%) of a white crystalline solid: mp. 233-235°C (recrystallized from ethyl acetate); IR (KBr) 3135, 2958, 1745, 1675, 1254; ¹H NMR (d_6 -DMSO) δ 11.90 (1H, s), 8.07 (1H, s), 7.23 (1H, s), 4.83 (2H, s), 3.69 (3H, s), 2.16 (3H, s).
5 Anal. Calcd for $C_{10}H_{11}N_3O_3$ 0.1H₂O: C, 53.85; H, 5.07; N, 18.84. Found: C, 53.85; H, 4.96; N, 18.81; MS(70eV.E.I.) m/e 222, 221 (M^+ , 100%), 189, 162, 133, 105.

10 2-(3,5-Dihydro-7-methyl-4-oxo-4H-pyrrolo[3,2-d]pyrimidin-3-yl)acetic acid, sodium salt (41). A suspension of 40 (354mg, 1.6mmol) in methanol (15ml) was treated with 0.5N sodium hydroxide (4.8ml) and the resulting mixture was stirred at 25°C for 1h. The 15 reaction mixture was filtered to afford the hemihydrate of 41 (354mg, 97%) as a white crystalline solid : mp. >340°C (recrystallized from methanol); IR (KBr) 3461, 3143, 1676, 1666, 1605, 1415; ¹H NMR(d_6 DMSO) δ 11.63 (1H, s), 7.83 (1H, s), 7.11 (1H, d, $J=2.0$), 4.24 (2H, s), 2.14 (3H, s). Anal. Calcd for $C_9H_{10}N_3O_3Na$. 0.5H₂O: C, 45.39; H, 3.81; N, 17.64. Found: C, 45.57; H, 4.05; N, 17.39.
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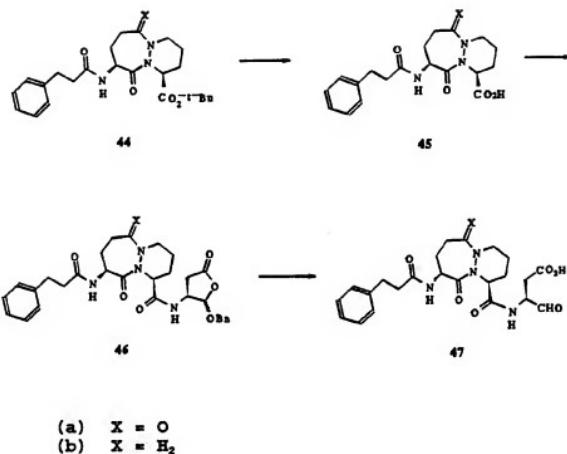
(2R,S, 3S) 2-(3,5-Dihydro-7-methyl-4-oxo-4H-pyrrolo[3,2-d]pyrimidin-3-yl)-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)acetamide (42). A suspension 25 of the sodium salt 41 (344mg, 1.5mmol) in dry DMF (15ml) was treated with ethyl dimethylaminopropyl carbodiimide hydrochloride (373mg, 1.95mmol) and 1-hydroxybenzo-triazole (405mg, 3.0mmol). The mixture was kept at 25°C for 1h then (2R,S, 3S) N-allyloxycarbonyl-3-amino-2-benzyloxy-5-oxotetrahydrofuran (437mg, 1.5mmol; Chapman, Bioorg. Med. Chem. Lett., 2, pp. 613-18 (1992)) and $(Ph_3P)_2PdCl_2$,
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- 168 -

(25mg) were added followed by the dropwise addition of n-tributyltin hydride (0.6ml, 2.25mmol). The resulting mixture was stirred at 25°C for 1h then water (20ml) was added. The mixture was extracted with ethyl acetate (3 x 15ml), and the combined organic extracts were washed with water (5ml), dried (MgSO_4), and concentrated to afford a mixture of diastereomers. Evaporation of the aqueous phase and purification of the residue by flash chromatography (5% methanol/chloroform) gave an additional quantity affording a total 182mg of 42 (31%) : m.p. 240-244°C; IR (KBr) 3274, 1772, 1691, 1664, 1562; ^1H NMR (d_6 -DMSO) δ 11.81 (1H, s), 8.85 (0.6H, d, $J=6.6$), 8.72 (0.4H, d, $J=7.4$), 7.98 (0.6H, s), 7.95 (0.4H, s), 7.40-7.30 (5H, m), 7.20 (1H, d, $J=2.2$), 5.61 (0.4H, d, $J=5.0$), 5.46 (s), 4.85-4.60 (m), 4.28 (m), 3.20-2.35 (2H, m), 2.16 (3H, s).

(3S)-3-[2-(3,5-Dihydro-7-methyl-4-oxo-4H-pyrrolo[3,2-d]pyrimidin-3-yl)-1-oxo-ethylamino]-4-oxobutanoic acid (43). A mixture of 42 (131mg, 0.33mmol), in methanol (50ml) and 10% palladium on carbon (100mg) was stirred vigorously under an atmosphere of hydrogen for 2h. An additional quantity of catalyst (100mg) was added and the mixture hydrogenated for a further 2h. The mixture was filtered through a 0.2 μm nylon membrane, and concentrated. The residue was recrystallized from methanol/diethyl ether to afford 79mg (78%) of 43 as a hygroscopic white solid: mp. 222-226°C; (decomp.); $[\alpha]_{D}^{22} +0.5$ (*c* 0.02, MeOH); IR (KBr) 3282, 1680, 1558, 1425, 1275; ^1H NMR (CD_3OD) δ 8.03 (1H, s), 7.18 (1H, d, $J=0.7$), 4.79-4.74 (2H, m), 4.63-4.59 (1H, 2 x d, $J=3.6$), 4.36-4.25 (1H, m), 2.78-2.39 (2H, m), 2.24 (3H, d, $J=0.7$). Anal. Calcd for $\text{C}_{13}\text{H}_{14}\text{N}_4\text{O}_5 \cdot 1.4\text{H}_2\text{O}$: C, 47.10; H, 5.12; N, 16.90. Found: C, 47.00; H, 4.79; N, 16.59.

- 169 -

FABMS m/e 307, 306 (M^+), 244, 207, 190, 152, 115 (100%).

5 (1S,9S) t-Butyl 6,10-dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (44a). To a solution of (1S,9S)t-butyl 9-amino-6,10-dioxo-octahydro-6H-pyridazino [1,2-a][1,2]diazepine-1-carboxylate (690mg; 2.32mmol; GB 2128984) in dioxane (16ml) and water (4ml) at 0°C was added solid sodium bicarbonate (292mg; 3.48mmol) followed by dropwise addition of 3-phenylpropionyl chloride (470mg; 2.78mmol). The mixture was stirred at room temperature for 2h then more sodium bicarbonate (200mg; 2.38mmol) and 3-phenylpropionyl chloride (100mg; 0.6mmol) was added. The mixture was stirred for a further 2h at room temperature, diluted with ethyl acetate (50ml), washed

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- 170 -

with saturated sodium bicarbonate (2 x 25ml) then dried (MgSO₄) and concentrated. The residue was purified by flash chromatography (0-50% ethyl acetate/chloroform) and finally crystallized by trituration with ether to afford 860mg (86%) of a white solid: mp. 137-138°C; [α]_D²³ -95.1° (c 0.549, CH₂Cl₂); IR (KBr) 3327, 1736, 1677, 1664, 1536, 1422, 1156; ¹H NMR (CDCl₃) δ 7.24 (5H, m), 6.50 (1H, d, J=7.5), 5.24 (1H, m), 4.90 (1H, m), 4.60 (1H, m), 3.44 (1H, m), 2.93 (2H, m), 2.84 (1H, m), 2.64 (1H, m), 2.54 (2H, m), 2.26 (2H, m), 1.70 (4H, m), 1.70 (9H, s). MS(FAB, m/z): 430 (M⁺ + 1), 374, 242, 105, 91.

(1S, 9S) t-Butyl octahydro-10-oxo-9-(3-phenylpropionylamino)-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxylate (44b), was prepared from (1S, 9S)-t-butyl 9-amino-octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (Attwood et al., J. Chem. Soc. Perkin 1, pp. 1011-19 (1986)) as for 44a, to afford 810mg (81%) of a colorless oil: [α]_D²³ - 33.5° (c 0.545, CH₂Cl₂); IR (film) 3334, 2935, 1737, 1728, 1659, 1642; ¹H NMR (CDCl₃) δ 7.24 (5H, m), 6.75 (1H, d, J=6.7), 5.27 (1H, m), 4.92 (1H, m), 3.39 (1H, m), 3.03 (4H, m), 2.55 (3H, m), 2.33 (1H, m), 2.17 (1H, m), 1.80 (5H, m), 1.47 (9H, s), 1.39 (1H, m). MS(FAB, m/z): 416 (M⁺ + 1), 360, 211, 143, 97.

(1S, 9S) 6,10-Dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid (45a). To a solution of (1S, 9S) t-butyl 6,10-dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (44a) (800mg; 1.863mmol) in dry dichloromethane (5ml) at 0°C was added trifluoroacetic acid (5ml). The solution was stirred

- 171 -

at room temperature for 3h then concentrated. Dry ether (10ml) was added to the residue then removed under vacuum. This process was repeated three times to afford a crystalline solid. The solid was triturated
5 with ether and filtered to afford 590mg (85%) of a white crystalline solid: mp. 196-197.5°C; $[\alpha]_D^{23}$ -129.5° (c 0.2, CH₃OH); IR (KBr) 3237, 1729, 1688, 1660, 1633, 1574, 1432, 1285, 1205; ¹H NMR (CD₃OD) δ 8.28 (1H, d, J=7.4), 7.22 (5H, m), 5.32 (1H, dd, J=5.9, 2.9), 4.75
10 (1H, m), 4.51 (1H, m), 3.50 (1H, m), 3.01 (1H, m), 2.91 (2H, m), 2.55 (2H, m), 2.29 (3H, m), 1.95 (2H, m), 1.71 (2H, m). Anal. Calcd for C₁₉H₂₂N₃O₅: C, 61.12; H, 6.21; N, 11.25. Found: C, 60.80; H, 6.28; N, 10.97. MS(FAB, m/z) 374 (M⁺ + 1), 242, 105, 91.

15 (1S, 9S) Octahydro-10-oxo-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a]-[1,2]diazepine-1-carboxylic acid (45b), was prepared from (1S, 9S) t-butyl octahydro-10-oxo-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (44b) by the method
20 described for compound 45a to afford 657mg (96%) of 45b as a crystalline solid: mp. 198-202°C; $[\alpha]_D^{23}$ -86.2° (c 0.5, CH₃OH); IR (KBr) 3294, 2939, 1729, 1645, 1620, 1574, 1453, 1214; ¹H NMR (CD₃OD) δ 7.92 (1H, d, J=7.9), 7.20 (5H, m), 5.29 (1H, m), 4.90 (1H, m), 3.47 (1H, m), 3.08 (2H, m), 2.90 (2H, m), 2.55 (3H, m), 2.36 (1H, m), 1.81 (5H, m), 1.43 (2H, m). MS(FAB, m/z) 360 (M⁺ + 1), 211, 143, 91.

25 [3S, 2R, S, (1S, 9S)] N-(2-Benzylxyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (46a). To a solution of (1S, 9S) 6,10-dioxo-octahydro-9-(3-phenyl-propionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid (45a) (662mg;

- 172 -

1.773mmol) in dry dichloromethane (9ml) and dry dimethyl formamide (3ml) at room temperature was added bis(triphenylphosphine)palladium chloride (30mg) and (3*S*, 2*R*, *S*)-3-allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydrofuran (Chapman, *Biorg. Med. Chem. Lett.*, 2, pp. 613-18 (1992)) (568mg; 1.95mmol) followed by dropwise addition of tri-n-butyltin hydride (1.19g; 4.09mmol). 1-Hydroxy-benzotriazole (479mg; 3.546mmol) was added to the mixture and the mixture was cooled to 0°C before addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (408mg; 2.128mmol). The mixture was stirred at room temperature for 3.25h then diluted with ethyl acetate (50ml), washed twice with dilute hydrochloric acid (20ml), twice with saturated sodium bicarbonate (20ml), once with brine then dried (MgSO_4) and concentrated. The resulting oil was purified by flash chromatography (0-100% ethyl acetate/chloroform) to afford 810mg (81%) of 46a as a mixture of anomers: mp. 92-94°C; IR (KBr) 3311, 1791, 1659, 1651, 1536; ^1H NMR (CDCl_3), δ 7.49, 6.56 (1H, 2d, $J=6.7$, 7.8), 7.29 (10H, m), 6.37, 6.18 (1H, 2d, $J=7.7$, 7.6), 5.56, 5.34 (1H, d, s, $J=5.2$), 5.08-4.47 (6H), 3.18-2.80 (5H), 2.62-2.28 (5H), 2.04-1.53 (5H). MS(FAB, m/z), 563 ($M^+ + 1$), 328, 149, 91.

[3*S*, 2*R*, *S*, (1*S*, 9*S*)] N-(2-Benzylxy-5-oxotetrahydrofuran-3-yl)-octahydro-10-oxo-9-(3-phenylpropionylamino)-6*H*-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (46b), was prepared from 45b by the method described for 46a to yield 790mg (96%) of a glass: m.p. 58-60°C; IR (KBr) 3316, 2940, 1793, 1678, 1641, 1523, 1453, 1120; ^1H NMR (CDCl_3), δ 7.28 (10H, m), 6.52, 6.42 (1H, 2d, $J=7.2$, 7.1), 5.53, 5.44 (1H, d, s, $J=5.2$), 5.35 (1H, m), 4.6-4.9, 4.34 (4H, m), 3.1-2.8 (6H, m), 2.6-2.1 (7H), 1.95-1.05 (5H).

- 173 -

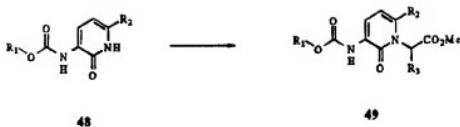
MS(FAB, m/z), 549 (M⁺ + 1), 400, 310, 279, 91.

[3S, (1S, 9S)] 3-(6,10-Dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (47a).

5 A mixture of [3S, 2R,S, (1S, 9S)] N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (46a) (205mg; 0.364mmol), 10 10% palladium on carbon (200mg) and methanol (20ml) was stirred under hydrogen at atmospheric pressure for 5h. The mixture was filtered then concentrated to yield 154mg (90%) of a glass: mp. 116-118°C; [α]_D²³ -140° (c 0.1, CH₃OH); IR (KBr) 3323 (br), 1783, 1731, 1658, 1539, 1455, 1425; ¹H NMR (CD₃OD) δ 7.21 (5H, m), 5.17 (1H, m), 4.73 (1H, m), 4.50 (2H, m), 4.23 (1H, m), 3.38 (1H, m), 3.06 (1H, m), 2.91 (2H, m), 2.73-2.18 (6H, m) and 2.01-1.59 (5H, m). Anal. Calcd for C₂₃H₂₇N₄O₇ + H₂O : C, 56.32; H, 6.16; N, 11.42. Found: C, 56.29; H, 6.11; N, 11.25. MS(FAB, m/z) 473 (M⁺ + 1), 176, 149, 105, 91.

20 [3S, (1S, 9S)] 3-(Octahydro-10-oxo-9-(3-phenylpropionylamino)-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (47b), 25 was prepared from 46b by the method described for 47a. The residue was purified by flash chromatography (0-10% methanol/chloroform) to afford 65mg (52%) of a glass; m.p. 87-90°C; [α]_D²³ -167.0° (c 0.1, methanol); IR (KBr) 3329, 2936, 1786, 1727, 1637; ¹H NMR (CD₃OD) δ 7.23 (5H, m), 5.29 (1H, m), 4.83 (1H, m), 4.59 (1H, d, J=3.6), 4.29 (1H, m), 3.3-3.0 (3H, m), 2.91 (2H, m), 2.70-2.34 (5H, m), 2.19 (2H, m), 1.75 (4H, m), 1.36 (2H, m). Anal. Calcd for C₂₃H₃₀N₄O₆ + 0.5H₂O: C, 59.09; H, 6.68; N, 11.98. Found: C, 58.97; 6.68; N, 11.73. MS(FAB, m/z) 459 (M⁺ + 1), 310, 149, 105, 91.

- 174 -



	R ₁	R ₂	R ₃
(a)	PhCH ₂	H	(S) Me
(b)	PhCH ₂	CH ₂ Ph	H
5 (c)	PhCH ₂	(CH ₂) ₂ Ph	H
(d)	PhCH ₂	nBu	H
(e)	PhCH ₂	Me	H
(f)	PhCH ₂	Ph	H
(g)	PhCH ₂	H	H
10 (h)	PhCH ₂	CH ₂ Ph	(S) -Me
(i)	Ph(CH ₂) ₂	CH ₂ Ph	H

Pyridones 48 were prepared by the method described by Damewood et al., J. Med. Chem., 37, pp. 3303-12 (1994)). Compound 48d is new.

15 3-Benzoyloxycarbonylamino-6-butyl-pyrid-2-one (48d), was isolated as a cream solid: mp. 158-160°C; IR (KBr) 3382, 2953, 2930, 2866, 1729, 1643, 1524, 1468, 1202, 1044; ¹H NMR (d_6 -DMSO) δ 8.26 (1H, s), 7.72 (1H, d), 7.39 (5H, m), 6.00 (1H, d), 5.14 (2H, s), 2.41 (2H, t), 1.52 (2H, m), 1.24 (2H, m), 0.87 (3H, t). Anal. Calcd for C₁₇H₂₀N₂O₃: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.69; H, 6.68; N, 9.20. MS CI M' = 300 (m) 28%.

25 (2S) Methyl 2-[3-benzoyloxycarbonylamino-1,2-dihydro-2-oxo-1-pyridyll]propionate (49a). Sodium hydride (80% oil dispersion) (0.35g, 11.64mmole) was added to a stirred mixture of 3-(benzoyloxycarbonylamino)pyrid-2-

- 175 -

one (48a) (2.58g, 10.58mmol) and tetrahydrofuran (100ml) at room temperature. The mixture was stirred for 10 mins. The resulting solution was added to a solution of 2(R) methyl-2((trifluoromethane) sulphonyloxy)propionate (2.5g, 10.58mmole; Feenstra et al., *Tetrahedron Lett.*, 28, pp. 1215-18 (1987)) in tetrahydrofuran (5ml) at room temperature during 10 mins. The mixture was stirred at room temperature for 80 mins then poured into ethyl acetate. The mixture was washed twice with 1M HCl, twice with aqueous sodium bicarbonate then brine. It was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (30% ethyl acetate/hexane) to afford 2.945g (84%) of a colorless solid: mp. 96-7°; $[\alpha]_D^{20}$ - 71.36 (c 2.5, $CHCl_2$); IR (KBr) 3370, 1764, 1729, 1648, 1602, 1564, 1523, 1515, 1503, 1449, 1359, 1203, 1064; 1H NMR ($CDCl_3$) δ 8.04 (1H, d, $J=7.2$), 7.86 (1H, s), 7.36 (5H, m), 6.98 (1H, dd, $J=7.1$, $J=1.7$), 6.30 (1H, t, $J=7.2$), 5.46 (1H, q, $J=7.4$), 5.20 (2H, s), 3.74 (3H, s), 1.66 (3H, d, $J=7.4$). Anal. Calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found: C, 61.49; H, 5.51; N, 8.41. MS(FAB, m/z) 331 ($M^+ + 1$), 299, 223, 196, 163, 91.

Methyl [6-benzyl-3-benzyloxycarbonylamino-1,2-dihydro-2-oxo-1-pyridyl]-acetate (49b). Sodium hydride (80% oil dispersion) (0.65g, 26.2mmole) was added to a stirred mixture of 6-benzyl-3(benzyloxycarbonylamino) pyrid-2-one (48b) (7.3g, 2.18mmol) and tetrahydrofuran (150ml) at room temperature. The mixture was stirred for 10mins, treated with methyl bromoacetate (2.5ml, 26.2mmol) and kept for 3h. The resulting mixture was poured onto a mixture of ice and 1M HCl. The resulting solid was filtered off then dissolved in dichloromethane. The resulting solution was dried

- 176 -

(MgSO₄), decolourized with charcoal and concentrated. The residue was purified by chromatography (2-5% ethyl acetate/dichloromethane) to afford 7.2g (81%) of colorless crystals: mp. 117-9°; IR (KBr) 3375, 1753, 1730, 1651, 1605, 1513, 1384, 1223, 1185, 1071; ¹H NMR (CDCl₃) δ 8.02 (1H, d, J=7.5), 7.78 (1H, s), 7.31 (8H, m), 7.10 (2H, m), 6.15 (1H, d, J=7.5), 5.20 (2H, s), 4.70 (2H, s), 3.88 (2H, s), 3.66 (3H, s).

The following compounds were prepared in a similar manner:

Methyl [3-benzyloxycarbonylamino-1,2-dihydro-2-oxo-6-phenethyl-1-pyridyll]-acetate (49c). 97% yield: m.p. 102-4°C. IR (KBr) 3245, 3232, 1741, 1725, 1648, 1600, 1526, 1216; ¹H NMR (d₆-DMSO) δ 8.45 (1H, s), 7.76 (1H, d, J = 7.6), 7.35 (10H, m), 6.15 (1H, d, J = 7.6), 5.15 (2H, s), 4.85 (2H, s), 3.68 (3H, s), 2.86 (4H, s).

Methyl [3-benzyloxycarbonylamino-6-butyl-1,2-dihydro-2-oxo-1-pyridyl]-acetate (49d). 90% yield: mp. 111-112°C; IR (KBr) 3393, 1738, 1731, 1645, 1598, 1517, 1225, 1208; ¹H NMR (d₆-DMSO) δ 8.39 (1H, s), 7.78 (1H, d, J = 7.7), 7.35 (5H, m), 6.17 (1H, d, J = 7.7), 5.15 (2H, s), 4.80 (2H, s), 3.67 (3H, s), 1.38 (6H, m), 0.89 (3H, t).

Methyl [3-benzyloxycarbonylamino-1,2-dihydro-6-methyl-2-oxo-1-pyridyl]-acetate (49e). 84% yield as a colorless solid: mp. 115-6°C; IR (KBr) 3246, 1740, 1725, 1649, 1598, 1573, 1535, 1417, 1365, 1259, 1219, 1193, 1090, 1068, 1006; ¹H NMR (d₆-DMSO) δ 8.40 (1H, s), 7.75 (1H, d, J = 7.6), 7.38 (5H, m), 6.20 (1H, d, J = 7.6), 5.15 (2H, s), 4.85 (2H, s), 3.68 (3H, s), 2.26 (3H, s).

- 177 -

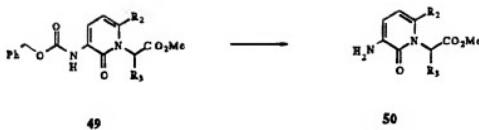
Methyl [3-benzyloxycarbonylamino-1,2-dihydro-6-phenyl-1-pyridyl]-acetate (49f). 67% yield as a colorless oil: IR (KBr) 3266, 1739, 1727, 1646, 1606, 1566, 1517, 1490, 1365, 1213, 1163, 1075; ¹H NMR (CDCl₃) δ 8.15 (1H, d), 7.85 (1H, s), 7.39 (10H, m), 6.22 (1H, d), 5.22 (2H, s), 4.57 (2H, s), 3.74 (3H, s).

Methyl [3-benzyloxycarbonylamino-1,2-dihydro-2-oxo-1-pyridyl]-acetate (49g). 80% yield as a colorless crystalline solid: m.p. 110-111°C. IR (KBr) 3385, 1745, 1726, 1650, 1601, 1512, 1502, 1378, 1369, 1358, 1215, 1195, 1162, 1067; ¹H NMR (CDCl₃) δ 8.06 (1H, d), 7.84 (1H, s), 7.36 (5H, m), 6.88 (1H, dd), 6.27 (1H, t), 5.20 (2H, s), 4.68 (2H, s), 3.78 (3H, s). Anal. Calcd for C₁₆H₁₆N₂O₅: C, 60.75; H, 5.10; N, 8.85. Found: C, 60.65; H, 5.15; N, 8.85. MS FAB (+)M⁺ = 317 (M + 1).

2 (S) Methyl 2-methyl-[6-benzyl-(3-benzyloxycarbonyl-amino)-1,2-dihydro-2-oxo-1-pyridyl]-acetate (49h), was prepared by the method used in the preparation of compound 49a to afford (58%) an oil; [α]_D²⁵ -25.0° (c 1, CH₂Cl₂); IR (KBr) 3381, 1736, 1650, 1604, 1513, 1218, 1190, 1068; ¹H NMR (CDCl₃) δ 7.97 (1H, d), 7.78 (1H, s), 7.4-7.14 (10H, m), 6.17 (1H, d), 5.19 (2H, s), 4.64 (1H, q), 3.98 (2H, s), 3.62 (3H, s), 1.31 (3H, d).

Methyl [6-benzyl-1,2-dihydro-2-oxo-3-(2-phenoxyethoxy)-carbonylamino-1-pyridyl]acetate (49i), was isolated (88%) as a colorless solid: mp. 130-133°C; IR (KBr) 3363, 1746, 1732, 1651, 1604, 1515, 1368, 1231, 1212, 1185; ¹H NMR (CDCl₃) δ 8.00 (1H, d, J = 7.0), 7.68 (1H, s), 7.36-7.10 (10H, m), 6.15 (1H, d, J = 7.6), 4.7 (2H, s), 4.38 (2H, t, J = 7.0), 3.88 (2H, s), 3.67 (3H, s), 2.98 (2H, t, J = 7).

- 178 -



2 (S) Methyl 2 [3-amino-1,2-dihydro-2-oxo-1-pyridyl]propionate (50a). A mixture of 2 (S) methyl-
5 2 [3-benzyloxycarbonylamino-1,2-dihydro-2-oxo-1-pyridyl]propionate (49a) (2.75g, 8.33mmol), methanol
(100ml), and 10% palladium on carbon (300mg) was
stirred under an atmosphere of hydrogen for 30min. The
mixiture was filtered and concentrated to afford 1.63g
10 (100%) of a colorless solid: ^1H NMR (d_6 -DMSO) δ 8.35
(1H, brs), 7.46 (1H, d), 7.22 (1H, d), 6.29 (1H, t),
5.22 (1H, q), 3.63 (3H, s), 1.55 (3H, d).

The following compounds were prepared in a similar manner:

15 Methyl [3-amino-6-benzyl-1,2-dihydro-2-oxo-1-pyridyl]acetate (50b). 100% yield as a grey solid: mp.
134-6°C; IR (KBr) 3418, 3312, 1723, 1658, 1596, 1548,
1435, 1290, 1245, 1011; ^1H NMR (d_6 -DMSO) δ 7.25 (5H, m),
6.45 (1H, d, J = 7.4), 5.92 (1H, d, J = 7.4), 5.00 (2H,
20 s), 4.63 (2H, s), 3.88 (2H, s), 3.51 (3H, s).

25 Methyl [3-amino-1,2-dihydro-2-oxo-6-phenethyl-1-pyridyl]acetate (50c). 99% yield as a viscous oil: IR
(KBr) 3456, 341, 2953, 1745, 1649, 1600, 1548, 1219;
 ^1H NMR (CDCl_3) δ 7.25 (5H, m), 6.51 (1H, d, J = 7.4),
5.92 (1H, d, J = 7.4), 4.79 (2H, s), 3.77 (3H, s), 2.80
(4H, m).

- 179 -

Methyl [3-amino-6-butyl-1,2-dihydro-2-oxo-1-pyridyl]acetate (50d). 97% as a brown solid: mp. 75-7°C; IR (KBr) 3437, 3342, 2955, 1745, 1655, 1609, 1550, 1432, 1301, 1222, 1200; ¹H NMR (CDCl₃) δ 6.53 (1H, d, J = 6.8), 5.93 (1H, d, J = 6.8), 4.81 (2H, s), 3.77 (3H, s), 2.44 (2H, t), 1.45 (4H, m), 0.93 (3H, t).

Methyl [3-amino-1,2-dihydro-6-methyl-2-oxo-1-pyridyl]acetate (50e), was isolated (100%) as a colorless crystalline solid: mp. 87-9°C; IR (KBr) 3442, 3326, 1735, 1647, 1600, 1549, 1434, 1407, 1383, 1366, 1225, 1209; ¹H NMR (d₆-DMSO) δ 6.40 (1H, d, J = 7.3), 5.93 (1H, d, J = 7.3), 4.86 (2H, s), 4.79 (2H, s), 3.67 (3H, s), 2.15 (3H, s).

Methyl [3-amino-1,2-dihydro-2-oxo-6-phenyl-1-pyridyl]acetate (50f), was isolated (86%) as a grey solid: mp. 207-9°C; IR (KBr) 3473, 3345, 1750, 1644, 1600, 1536, 1443, 1366, 1309, 1212, 1184, 1156; ¹H NMR (d₆-DMSO) δ 7.30 (5H, m), 6.54 (1H, d), 6.03 (1H, d), 5.25 (2H, s), 4.49 (2H, s), 3.61 (3H, s).

Methyl [3-amino-1,2-dihydro-2-oxo-1-pyridyl]acetate (50g), was obtained as a colorless oil and used immediately in the next step.

2(S) Methyl 2-methyl-[3-amino-6-benzyl-1,2-dihydro-2-oxo-1-pyridyl]acetate (50h), was isolated (69%) as a colorless oil: IR (film) 3354, 1743, 1646, 1600, 1548, 1494, 1455, 1309, 1268, 1227, 113; ¹H NMR (C₆D₆) δ 7.29-6.76 (5H, m), 5.86 (1H, d, J = 7.2), 5.51 (1H, d, J = 7.2), 4.43 (1H, q, J = 6.7), 3.69 (2H, s), 3.41 (2H, s), 3.36 (3H, s), 1.43 (3H, d, J = 6.7).

- 180 -



	R ₁	R ₂	R ₃
	(a) Ph(CH ₂) ₂ CO	H	(S)Me
	(b) Ph(CH ₂) ₂ CO	CH ₂ Ph	H
5	(c) Ph(CH ₂) ₂ CO	(CH ₂) ₂ Ph	H
	(d) Ph(CH ₂) ₂ CO	nBu	H
	(e) Ph(CH ₂) ₂ CO	Me	H
	(f) Ph(CH ₂) ₂ CO	Ph	H
	(g) Ph(CH ₂) ₂ CO	H	H
10	(h) Ph(CH ₂) ₂ CO	CH ₂ Ph	(S)-Me or (R,S)-Me
	(i) AcTyr	CH ₂ Ph	H
	(j) Ph(CH ₂) ₂ SO ₂	CH ₂ Ph	H
	(k) Ph(CH ₂) ₂ OCO	CH ₂ Ph	H
15	(l) Ph(CH ₂) ₃ CO	CH ₂ Ph	H

2(S) Methyl 2-[1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]- propionate (51a). 3-Phenylpropionyl chloride (1.5g, 9mmol) was added dropwise to a stirred mixture of 2S methyl-2-[3-amino-1,2-dihydro-2-oxo-1-pyridyl]propionate (50a) (1.63g, 8.33mmol), dioxane (60ml), water (15ml) and sodium bicarbonate (1.54g, 16.7mmol). The mixture was kept for 1h then extracted with ethyl acetate. The extracts were washed with aqueous sodium bicarbonate, dried (MgSO₄) and concentrated. The resulting red oil was purified by flash chromatography to afford 2.54g (93%) of an oil:

- 181 -

[α]_D²⁰ -68°C (1, CH₂Cl₂); IR (CH₂Cl₂) 3369, 1747, 1690, 1650, 1602, 1512, 1267, 1260, 1217; ¹H NMR (CDCl₃) δ 8.41 (1H, dd), 8.36 (1H, s), 7.24 (5H, m), 7.02 (1H, dd), 6.32 (1H, t), 5.44 (1H, q), 3.75 (3H, s), 3.03 (2H, t), 2.70 (2H, t), 1.66 (3H, d). FAB M+ = 329 (M + 1), 197, 165, 131, 110, 91.

The following compounds were prepared in a similar manner:

Methyl [6-benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-acetate (51b), was isolated (93%) as crystals: mp. 95-7°C; IR (KBr) 3265, 1747, 1686, 1642, 1590, 1563, 1511, 1454, 1401, 1220, 1183, 1133; ¹H NMR (CDCl₃) δ 8.39 (1H, d, J = 7.7), 8.27 (1H, s), 7.21 (10H, m), 6.17 (1H, d, J = 7.7), 4.70 (2H, s), 3.89 (2H, s), 3.67 (3H, s), 3.02 (2H, m), 2.70 (2H, m).

Methyl [1,2-dihydro-2-oxo-6-phenethyl-3-(3-phenylpropionyl)amino-1-pyridyl]-acetate (51c), was isolated (81%) as colorless crystals: mp. 105-8°C; IR (KBr) 3378, 1746, 1680, 1646, 1597, 1517, 1221; ¹H NMR (CDCl₃) δ 8.34 (1H, d, J = 7.7), 8.25 (1H, s), 7.23 (10H, m), 6.11 (1H, d, J = 7.7), 4.77 (2H, s), 3.78 (3H, s), 2.88 (8H, m).

Methyl [6-butyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-acetate (51d), was isolated (88%) as colorless crystals: mp. 84-5°C; IR (KBr) 3345, 2958, 2930, 1756, 1693, 1650, 1602, 1510, 1227, 1180, 1137; ¹H NMR (CDCl₃) δ 8.34 (1H, d, J = 7.7), 8.22 (1H, s), 7.26 (5H, m), 6.12 (1H, d, J = 7.7), 4.80 (2H, s), 3.79 (3H, s), 3.03 (2H, t), 2.68 (2H, t), 2.50 (2H, t), 1.46 (4H, m), 0.95 (3H, t).

- 182 -

Methyl [1,2-dihydro-6-methyl-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-acetate (51e), was isolated (100%) as a pale yellow oil: IR (film) 3264, 1745, 1691, 1644, 1587, 1566, 1518, 1495, 1400, 1215, 1183, 1136; ¹H NMR (CDCl₃) δ 8.33 (1H, d, J = 7.6), 7.26 (5H, m), 6.13 (1H, d, J = 7.6), 4.83 (2H, s), 3.79 (3H, s), 3.03 (2H, m), 2.69 (2H, m), 2.28 (3H, s).

Methyl [1,2-dihydro-2-oxo-6-phenyl-3-(3-phenylpropionyl)amino-1-pyridyl]-acetate (51f), was isolated (99%) as a pale yellow oil: IR (film) 3365, 3299, 1751, 1689, 1643, 1600, 1563, 1519, 1493, 1419, 1370, 1224; ¹H NMR (CDCl₃) δ 8.46 (1H, d, J = 7.7), 8.32 (1H, s), 7.32 (10H, m), 6.24 (2H, d, J = 7.7), 4.57 (2H, s), 3.73 (3H, s), 3.06 (2H, m), 2.72 (2H, m).

Methyl [1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-acetate (51g), was isolated (81%) as an oil: IR (film) 3330, 1753, 1689, 1650, 1600, 1560, 1517, 1374, 1225, 1208; ¹H NMR (CDCl₃) δ 8.43 (1H, dd, J = 7.4, 1.7), 8.33 (1H, s), 7.28 (5H, m), 6.92 (1H, dd, J = 6.9, 1.7), 6.29 (1H, t), 4.67 (2H, s), 3.79 (3H, s), 3.04 (2H, m), 2.70 (2H, m). MS FAB (+) M+ = 315 (M + 1).

2(S) Methyl 2-methyl-[6-benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-acetate (51h), was isolated (93%) as a colorless oil; [α]_D³⁰ -19° (c 1, CH₂Cl₂); IR (film) 3354, 3313, 3028, 2950, 1745, 1687, 1645, 1600, 1567, 1514, 1454, 1225; ¹H NMR (CDCl₃) δ 8.35 (1H, d, J = 7.5), 8.26 (1H, s), 7.27 (10H, m), 6.20 (1H, d, J = 7.5), 4.65 (1H, q, J = 6.8), 3.99 (2H, s), 3.71 (3H, s), 3.03 (2H, m), 2.68 (2H, m), 1.31 (3H, d, J = 6.8).

Methyl [3-(N-acetyl-O-benzyl-L-tyrosine)amino-6-benzyl-
1,2-dihydro-2-oxo-pyridyl]acetate (51i). A stirred
mixture of methyl [3-amino-6-benzyl-1,2-dihydro-2-oxo-
1-pyridyl]acetate (100mg, 0.367mmol), Boc-Tyr(Bn)-OH
5 (136mg, 0.367mmol), dimethylformamide (1ml),
diisopropylethylamine (0.25ml, 1.468mmol) and 2-(1H-
benzotriazol-1-yl)-1,1,3,3-tetramethyluronium
hexafluorophosphate (118mg, 0.367mmol) was kept
overnight at room temperature. The mixture was diluted
10 with ethyl acetate, washed twice with 1M hydrochloric
acid, twice with aqueous sodium bicarbonate, once with
brine, then dried (MgSO_4) and concentrated. The residue
was purified by flash chromatography (10% ethyl
acetate/dichloromethane) to afford a 162mg (70%) of a
15 colorless oil. The oil (160mg, 0.255mmol) was
dissolved in dichloromethane (1ml) and treated with
trifluoroacetic acid (1ml) at 0°C. The resulting
solution was allowed to reach room temperature during
40min then evaporated to dryness at 30°C. The residue
20 was dissolved in dichloromethane then evaporated to
dryness again. This procedure was repeated three
times. The residue was dissolved in pyridine (0.5ml)
and treated with acetic anhydride (0.03ml, 0.3mmol) at
0°C. The resulting mixture was allowed to reach room
25 temperature and kept for 3.5h. It was diluted with
ethyl acetate, washed twice with 1M hydrochloric acid,
twice with aqueous sodium bicarbonate, dried (MgSO_4) and
concentrated to afford 128mg (86%) of a colorless oil:
IR (film) 3290, 1751, 1649, 1602, 1568, 1513, 1455,
30 1438, 1375, 1224, 1179; ^1H NMR (CDCl_3) δ 8.78 (1H, s),
8.33 (1H, d, $J = 7.6$), 7.33 (8H, m), 7.11 (4H, m), 6.86
(2H, d, $J = 8.5$), 6.47 (1H, d, $J = 7.6$), 6.12 (1H, d, J
= 7.6), 4.99 (2H, s), 4.85 (1H, m), 4.69 (2H, s), 3.87
(2H, s), 3.62 (3H, s), 3.08 (2H, m), 1.96 (3H, s).

- 184 -

5 Methyl [6-benzyl-1,2-dihydro-2-oxo-3-(2-phenylethanedisulphonyl)amino-1-pyridyl]-acetate (51j).
 10 2-Phenylethanedisulphonyl chloride (Zhong et al., *J. Am. Chem. Soc.*, 113, pp. 2259-63 (1991)) was added to a stirred mixture of methyl [3-amino-6-benzyl-2-oxo-1,2-dihydro-1-pyridyl]-acetate (49b) (1.0g, 3.67mmol), dichloromethane (15ml) and triethylamine (1.0ml, 7.34mmol). The mixture was kept overnight then poured into ethyl acetate. The resulting mixture was washed twice with aqueous sodium bicarbonate, three times with 1M hydrochloric acid, then brine. It was dried (MgSO_4) and concentrated. The resulting pale brown solid was purified by flash chromatography (10% ethyl acetate/dichloromethane) to afford 1.25g (77%) of a pale yellow solid: m.p. 92-4°C; IR (KBr) 3181, 1737, 1646, 1595, 1565, 1454, 1241, 1220, 1150; ^1H NMR (CDCl_3) δ 7.53 (1H, d, $J = 7.5$), 7.29 (10H, m), 6.10 (1H, d, $J = 7.5$), 4.75 (2H, s), 3.89 (2H, s), 3.67 (3H, s), 3.34 (2H, m), 3.14 (2H, m).

20 Methyl [6-benzyl-1,2-dihydro-2-oxo-3-(4-phenylbutyryl)amino-1-pyridyl]-acetate (51l), was isolated (74%) as colorless crystals: mp. 93-95°C; IR (KBr) 3285, 1747, 1683, 1642, 1591, 1563, 1512, 1455, 1220, 1181; ^1H NMR (CDCl_3) δ 8.39 (1H, d, $J = 7.6$), 8.24 (1H, s), 7.2 (10H, m), 6.18 (1H, d, $J = 7.6$), 4.7 (2H, s), 3.90 (2H, s), 3.67 (3H, s), 2.69 (2H, t), 2.40 (2H, t), 2.04 (2H, m).



- 185 -

2 (*S*) 2-[1,2-Dihydro-2-oxo-3-(3-phenylpropionyl)amino]-
1-pyridyl]propionic acid (52a). 1M Sodium hydroxide
(15ml, 15mmol) was added to a stirred solution of 2 (*S*)
methyl 2-[1,2-dihydro-2-oxo-3(3-phenylpropionyl)amino-
5 pyridyl]propionate (51a) (2.39g, 7.3mmol) in methanol
(30ml) at 0°C. The mixture was kept at this
temperature for 2h, acidified with 1M hydrochloric acid
(15.1ml) and extracted with ethyl acetate. The
extracts were washed with brine, dried (MgSO_4) and
concentrated to afford 1.98g (87%) of a colorless
10 solid: $[\alpha]_D^{20}$ -75° (1, CH_2Cl_2); IR (KBr) 3301, 1724,
1693, 1637, 1563, 1523, 1453, 1233, 1216, 765; ^1H NMR
(CDCl_3) δ 8.47 (2H, m), 7.20 (5H, m), 7.03 (1H, d), 6.36
(1H, t), 5.35 (1H, q), 3.01 (2H, m), 2.70 (2H, m), 1.69
15 (3H, m).

The following compounds were prepared in a similar
manner:

[6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-
20 1-pyridyl]acetic acid (52b), was isolated (100%) as a
pale amber oil: IR (film) 3291, 1738, 1686, 1644,
1591, 1554, 1519, 1496, 1454, 1403, 1215, 1182; ^1H NMR
(CDCl_3) δ 8.44 (1H, d, $J = 7.8$), 8.4 (1H, s), 7.21 (10H,
m), 6.19 (1H, d, $J = 7.8$), 4.71 (2H, s), 3.90 (2H, s),
2.99 (2H, m), 2.71 (2H, m).

25 [1,2-Dihydro-2-oxo-6-phenethyl-3-(3-phenylpropionyl)
amino-1-pyridyl]acetic acid (52c), was isolated (94%)
as a beige solid: mp. 214-6°C; IR (KBr) 3289, 1740,
1680, 1640; ^1H NMR (d_6 -DMSO) δ 9.24 (1H, s), 8.14 (1H,
d, $J = 7.7$), 7.22 (10H, m), 6.11 (1H, d, $J = 7.8$), 4.78
30 (2H, s), 2.81 (8H, m).

- 186 -

[6-Butyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-
1-pyridyl]acetic acid (52d), was isolated (99%) as a
pale brown solid: mp. 132-4°C; IR (KBr) 3286, 1739,
1676, 1641, 1584, 1555, 1535, 1455, 1414, 1249, 1227,
5 1204; ¹H NMR (CDCl₃) δ 8.42 (1H, d, J = 7.8), 8.37 (1H,
s), 7.24 (5H, m), 6.19 (1H, d, J = 7.8), 4.82 (2H, s),
3.55 (1H, s), 3.00 (2H, t), 2.67 (2H, t), 2.53 (2H, t),
1.41 (4H, m), 0.94 (3H, t).

[1,2-Dihydro-6-methyl-2-oxo-3-(3-phenylpropionyl)amino-
10 1-pyridyl]acetic acid (52e), was isolated as a solid
(100%): mp. 159-61°C; IR (KBr) 3335, 1731, 1686, 1642,
1536, 1516, 1430, 1420, 1401, 1222, 1195; ¹H NMR (d₆-
DMSO) δ 9.21 (1H, s), 8.13 (1H, d, J = 7.6), 7.20 (5H,
m), 6.15 (1H, d, J = 7.6), 4.77 (2H, s), 2.87 (2H, m),
15 2.70 (2H, m), 2.25 (3H, s).

[1,2-Dihydro-2-oxo-6-phenyl-3-(3-phenylpropionyl)amino-
1-pyridyl]acetic acid (52f), was isolated (100%) as a
pale yellow foam: IR (KBr) 3271, 1747, 1683, 1634,
1580, 1536, 1490, 1406, 1392, 1365, 1235, 1219; ¹H NMR
20 (CDCl₃) δ 8.52 (1H, d, J = 7.7), 7.31 (10H, m), 6.48
(2H, s), 6.30 (1H, d, J = 7.7), 4.60 (2H, s), 3.03 (2H,
m), 2.71 (2H, m).

[1,2-Dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-
pyridyl]acetic acid (52g), was isolated (94%) as a
colorless solid: mp. 195-7°C; IR (KBr) 3324, 1724,
1693, 1644, 1569, 1555, 1512, 1427, 1370, 1240; ¹H NMR
(d₆-DMSO) δ 9.31 (1H, s), 8.23 (1H, d, J = 6.8), 7.36
(1H, dd, J = 6.8, 1.71), 7.25 (5H, m), 6.25 (1H, t),
4.66 (2H, s), 2.84 (4H, m).

30 2(R,S) 2-[6-Benzyl-1,2-dihydro-2-oxo-3-(3-
phenylpropionyl)amino-1-pyridyl]-propionic acid (52h),

- 187 -

was prepared by hydrolysis of compound 5lh in aqueous tetrahydrofuran during 5 h at 40°C to afford (95%) as a yellow oil: IR (film) 3330, 1734, 1686, 1643, 1600, 1587, 1553, 1524, 1498, 1208; ¹H NMR (d_6 -DMSO) δ 9.29 (1H, s), 8.18 (1H, d, J = 7.6), 7.21 (10H, m), 6.22 (1H, d, J = 7.6), 4.82 (1H, q, J = 6.6), 4.08 (2H, m), 2.76 (4H, m), 1.05 (3H, d, J = 6.6).

[3-(Acetyl-Tyr(Bn))amino-6-benzyl-1,2-dihydro-2-oxo-1-pyridyl]acetic acid (52i), was isolated (93%) as a foam: IR (KBr) 3302, 1731, 1646, 1603, 1562, 1512, 1454, 1428, 1379, 1231, 1178; ¹H NMR ($CDCl_3$) δ 9.48 (1H, s), 8.36 (1H, d, J = 7.6), 7.30 (8H, m), 7.10 (2H, m), 6.85 (2H, d, J = 8.3), 6.91 (2H, d, J = 8.3), 6.71 (1H, d, J 7.6), 4.95 (1H, m), 4.90 (2H, s), 4.68 (2H, s), 3.92 (2H, s), 3.17-2.83 (2H, m), 1.92 (3H, s).

[6-Benzyl-1,2-dihydro-2-oxo-3-(2-phenylethanesulphonyl)amino-1-pyridyl]acetic acid (52j), was isolated (100%) as a colorless solid: mp. 165-7°C; IR (KBr) 3174, 1760, 1646, 1593, 1567, 1497, 1453, 1424, 1326, 1225, 1140, 1127; ¹H NMR (d_6 -DMSO) δ 13.09 (1H, s), 9.08 (1H, s), 7.30 (11H, m), 6.02 (1H, d), 4.68 (2H, s), 4.99 (2H, s), 3.29 (2H, m), 3.03 (2H, m).

[6-Benzyl-1,2-dihydro-2-oxo-3-(2-phenylethoxy)carbonylamino-1-pyridyl]acetic acid (52k), was prepared (70%) by hydrolysis of compound 49i during 1 h at 60°C: IR (CH_2Cl_2) 1797, 1689, 1649, 1601, 1512, 734; ¹H NMR ($CDCl_3$) δ 8.39 (1H, s), 8.03 (1H, d), 7.81 (1H, s), 7.33-7.07 (10H, m), 6.13 (1H, d, J = 7.8), 4.72 (2H, s), 4.33 (2H, t, J = 7.0), 3.86 (2H, s), 2.93 (2H, t, J = 7.0).

- 188 -

[6-Benzyl-1,2-dihydro-2-oxo-3-(4-phenylbutyryl)amino-1-pyridyl]acetic acid (521), was isolated (100%) as a white foam: m.p. 159-161°C; IR (KBr) 3373-3310, 1787, 1726, 1691, 1649, 1599, 1567, 1517, 1367, 1215; ¹H NMR (CDCl₃) δ 8.43 (1H, d, *J* = 7.7), 8.25 (1H, s), 7.37-7.09 (10H, m), 6.21 (1H, d, *J* = 7.7), 4.73 (2H, s), 4.15 (3H, s), 3.91 (2H, s), 2.67 (2H, t), 2.39 (2H, t), 2.02 (2H, m).



10 2(S), N-3(S) 2-[1,2-Dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-N-(2-benzyloxy-5-exotetrahydrofuran-3-yl)propionamide (53a). Tri-n-butyltin hydride (1.7ml, 6.3mmol) was added dropwise to a stirred mixture of 2(S)-2-[1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]propionic acid (52a) (1.1g, 3.49mmol), 3(S), 2(R,S) 3-allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydrofuran (1.02g, 3.49mmol; Chapman, *Biorg. Med. Chem. Lett.*, 2, pp. 613-18 (1992)), bis(triphenylphosphine)palladium (II) chloride (55mg), dichloromethane (35ml) and dimethylformamide (1ml). The resulting mixture was stirred for 5 min. then 1-hydroxybenzotriazole (946mg, 7mmol) was added. The mixture was cooled to 0°C before the addition of 1-(3-dimethylaminopropyl)-2-ethylcarbodiimide hydrochloride (740mg, 3.84mmol). The mixture was kept overnight at room temperature then poured into ethyl acetate. The mixture was washed twice with 1M hydrochloric acid, twice with aqueous sodium bicarbonate, then brine. The mixture was dried (MgSO₄)

- 189 -

and concentrated. The residue was triturated with pentane. The remaining solid was purified by flash chromatography (40-60% ethyl acetate/hexane) to afford 1.28g (73%) of colorless solid: IR (KBr) 1796, 1692, 1647, 1595, 1557, 1512, 1119; ¹H NMR (d_6 -DMSO) δ 9.28, 9.26 (1H, 2 x s), 8.77, 8.69 (1H, 2 x d), 8.24, 8.20 (1H, 2 x dd), 7.20 (11H, m), 6.31, 6.26 (1H, 2 x t), 5.65 (0.5H, d), 5.46 (0.5H, d), 5.41, 5.28 (1H, 2 x q), 4.7 (2.5H, m), 4.24 (0.5H, t), 3.24 (2H, m), 2.80 (4H, m), 1.51, 1.46 (3H, 2 x d).

The following compounds were prepared in a similar manner:

N(3(S)) 2-[6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)acetamide (53b), was obtained (86%) as a foam: IR (KBr) 3345, 3297, 1807, 1791, 1688, 1679, 1650, 1602, 1554, 1525, 1497, 1453, 1372, 1257, 1119; ¹H NMR (d_6 -DMSO) δ 9.25 (0.5H, s), 9.23 (0.5H, s), 8.75 (0.5H, d, J = 6.5), 8.67 (0.5H, d, J = 7.4), 8.18 (1H, 2d), 7.21 (15H, m), 6.07 (1H, 2d), 5.65 (0.5H, d, J = 5.0), 5.38 (0.5H, s), 4.83-4.45 (4.5H, m), 4.19 (0.5H, m), 3.94, 3.83 (2H, m), 3.10-2.31 (6H, m).

N(3(S)) 2[1,2-Dihydro-2-oxo-6-phenethyl-3-(3-phenylpropionyl)amino-1-pyridyl]-N-(2-benzyloxy-5-oxotetrahydrofuran-4-yl)acetamide (53c), was obtained (74%) as a mixture of anomers: ¹H NMR (d_6 -DMSO) δ 9.71 (1H, d), 9.41 (0.5H, d), 9.25 (0.5H, d), 8.64 (1H, d, J = 7.7), 7.75 (15H, m), 6.61 (1H, 2d), 6.11 (0.5H, d), 5.93 (0.5H, s), 5.17 (5H, m), 4.77 (0.5H, m), 3.68-2.94 (2H, m), 3.32 (8H, m).

- 190 -

- N(3(S)) 2[6-Butyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)acetamide (53d), was obtained (74%) as a mixture of anomers: IR (KBr) 3300, 1791, 1689, 1645, 1597, 1566, 1546, 1514, 1454, 1417, 1378; ¹H NMR (CDCl₃) δ 8.38 (1H, d, J = 7.7), 8.13 (1H, s), 7.30 (10H, m), 6.18 (1H, t), 5.47 (0.5H, d, J = 5.2), 5.43 (0.5H, s), 4.75 (4.5H, m), 4.38 (0.5H, m), 3.08-2.35 (8H, m), 1.43 (4H, m), 0.95 (3H, t).
- N(3(S)) 2[1,2-Dihydro-6-methyl-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)acetamide (53e), was obtained (67%) as a mixture of anomers: IR (KBr) 3282, 1774, 1667, 1651, 1596, 1561, 1556, 1498, 1265, 1254, 1236, 1199, 1143; ¹H NMR (d₆-DMSO) δ 9.17 and 9.15 (1H, 2 x s), 8.89 (0.5H, d, J = 6.5), 8.73 (0.5H, d, J = 7.4), 7.25 (10H, m), 6.13 (1H, t), 5.64 (0.5H, d, J = 5.0), 5.45 (0.5H, s), 4.89-4.61 (4.5H, m), 4.26 (0.5H, m), 3.17-2.36 (6H, m), 2.23 and 2.15 (3H, 2s).
- N(3(S)) 2-[1,2-Dihydro-2-oxo-6-phenyl-3-(3-phenylpropionyl)amino-1-pyridyl]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)acetamide (53f), was obtained (73%) as a mixture of anomers: IR (KBr) 3296, 1792, 1691, 1643, 1595, 1561, 1514, 1489, 1453, 1420, 1373, 1230, 1118; ¹H NMR (d₆-DMSO) δ 9.40, 9.36 (1H, 2s), 8.70 (0.5H, d, J = 7.6), 8.52 (0.5H, d, J = 7.5), 8.29 (1H, dd), 7.25 (15H, m), 6.20 (1H, d, J = 7.6), 5.61 (0.5H, d, J = 5.0), 5.28 (0.5H, s), 4.78-4.20 (5H, m), 3.12-2.24 (6H, m).
- N(3(S)) 2-[1,2-Dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)acetamide (53g), was obtained (70%) as a mixture of

- 191 -

- anomers: IR (KBr) 3336, 3290, 1791, 1691, 1646, 1595,
1582, 1556, 1518, 1454, 1376, 1351, 1150, 1122; ^1H NMR
(d_6 -DMSO) δ 9.26 (1H, 2s), 8.86 (0.5H, d, J = 6.4), 8.67
(0.5H, d, J = 7.5), 8.23 (1H, m), 7.40-7.13 (11H, m),
5 6.24 (1H, 2t, J = 7.2), 5.61 (0.5H, d, J = 5.0), 5.44
(0.5H, s), 4.83-4.59 (2.5H, m), 4.25 (0.5H, m), 3.15-
2.34 (2H, m), 2.91-2.70 (4H, m). Anal. Calc. for
 $\text{C}_{27}\text{H}_{27}\text{N}_3\text{O}_6 \text{ H}_2\text{O}$: C, 63.90; H, 5.76; N, 8.28. Found: C
63.70; H, 5.68; N, 8.22. MS FAB M^+ = 490 ($\text{M} + 1$).
- 10 2(R, S), N(3(S)) 2-[6-Benzyl-1,2-dihydro-2-oxo-3-(3-
phenylpropionyl)amino-1-pyridyl]-N-(2-benzyloxy-5-
oxotetrahydrofuran-3-yl)propionamide (53h), was
obtained (89%) as a mixture of diastereomers. Data is
given for a single diastereomer: IR (film) 3356, 1788,
1577, 1645, 1602, 1517, 1455, 1377, 1203, 1167, 1120;
15 ^1H NMR (CDCl_3) δ 8.34 (1H, d, J = 7.6), 8.19 (1H, s),
7.38-7.13 (10H, m), 6.26 (1H, d, J = 7.6), 5.58 (1H,
t), 5.31, 5.24 (1H, 2 x s), 4.62 (2H, 2q), 4.60 (1H,
m), 4.27 (1H, m), 2.98, 2.68 (4H, 2m), 3.0-2.0 (2H, m),
20 1.42 (3H, d).
- N(3(S)) 2-[6-Benzyl-1,2-dihydro-2-oxo-3-(N-acetyl-1-O-
benzyltyrosinyl)amino-1-pyridyl]-N-(2-benzyloxy-5-
oxotetrahydrofuran-3-yl)acetamide (53i), was obtained
(76%) as a mixture of anomers: IR (KBr) 1794, 1698,
25 1651, 1612, 1514, 1454, 1374, 1247, 1177, 1126; ^1H NMR
(d_6 -DMSO) δ 9.34, 9.31 (2 x 0.5H, 2s), 8.71 (1H, 2d),
8.38 (1H, m), 8.17 (1H, d), 7.48-6.88 (19H, m), 6.08
(1H, 2d), 5.65 (0.5H, d, J = 5.0), 5.40 (0.5H, s), 5.04
(2H, s), 4.68 (5.5H, m), 4.15 (0.5H, m), 3.95, 3.84
30 (2H, s + abq), 3.20-2.40 (4H, m), 1.78 (3H, s).

- 192 -

N(3(S)) 2-[6-Benzyl-1,2-dihydro-2-oxo-3-(2-phenylethanesulphonyl)amino-1-pyridyl]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)acetamide (53j), was obtained (78%) as a mixture of anomers: IR (KBr) 3344, 1792, 5 1691, 1647, 1599, 1566, 1454, 1365, 1150, 1121, 973; ¹H NMR (d_6 -DMSO) δ 9.02, 8.99 (1H, 2s), 8.80 (0.5H, d, J = 6.4), 8.70 (0.5H, d, J = 7.4), 7.26 (15H, m), 6.00 (1H, dd), 5.63 (0.5H, d, J = 5.0), 5.39 (0.5H, s), 4.68 (4.5H, m), 4.18 (0.5H, m), 3.90 (2H, m), 3.30-2.30 (6H, 10 m).

N(3(S)) 2-[6-Benzyl-1,2-dihydro-2-oxo-3-(2-phenylethoxy)carbonylamino-1-pyridyl]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)acetamide (53k), was obtained (78%) as a mixture of anomers: IR (KBr) 3386, 1794, 15 1726, 1650, 1603, 1518, 1366, 1214, 699; ¹H NMR (CDCl₃) δ 8.03 (1H, bd), 7.63, 7.61 (1H, 2 x s), 7.34-7.04 (15H, m), 6.21, 6.18 (1H, 2d), 5.44 (0.5H, d, J = 5.4), 5.37 (0.5H, s), 4.85, 4.83 (1H, 2d, J = 11.6, 11.5), 4.61-4.48, 4.32 (4H, 2m), 4.4 (2H, t), 4.08, 4.03 (2H, 20 2bs), 3.07-2.78 (3H, m), 2.47-2.30 (1H, m).

N(3(S)) 2-[6-Benzyl-1,2-dihydro-2-oxo-3-(4-phenylbutyryl)amino-1-pyridyl]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)acetamide (53l), was obtained (86%) as a colorless oil: IR (CH₂Cl₂) 1797, 1689, 1649, 25 1601, 1512, 734; ¹H NMR (CDCl₃) δ 8.42, 8.40 (1H, 2d, J = 7.6), 7.35-7.07 (15H, m), 6.21, 6.19 (1H, 2d, J = 7.6), 5.44 (0.5H, d), 5.37 (0.5H, s), 4.84, 4.81 (1H, 2d, J = 11.7, 11.4), 4.73-4.48, 4.34 (4H, 2m), 4.05 (2H, m), 3.05-2.63, 2.46-2.30 (6H, 2m), 2.01 (2H, m).

- 193 -



	R ₁	R ₂	R ₃
	(a) Ph(CH ₂) ₂ CO	H	(S)Me
	(b) Ph(CH ₂) ₂ CO	CH ₂ Ph	H
	(c) Ph(CH ₂) ₂ CO	(CH ₂) ₂ Ph	H
5	(d) Ph(CH ₂) ₂ CO	nBu	H
	(e) Ph(CH ₂) ₂ CO	Me	H
	(f) Ph(CH ₂) ₂ CO	Ph	H
	(g) Ph(CH ₂) ₂ CO	H	H
	(h) Ph(CH ₂) ₂ CO	CH ₂ Ph	(R,S)-Me
10	(i) AcTyr	CH ₂ Ph	H
	(j) Ph(CH ₂) ₂ SO ₂	CH ₂ Ph	H
	(k) Ph(CH ₂) ₂ OOC	CH ₂ Ph	H
	(l) Ph(CH ₂) ₃ CO	CH ₂ Ph	H

3(S), N(2(S)) 3-(2-(1,2-Dihydro-2-oxo-3-(3-phenylpropionylamino-1-pyridyl)-propionylamino)-4-oxo-butanoic acid (54a; E). A mixture of 2(S), N(3(S)) 2-[1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-N(2-benzyloxy-5-oxotetrahydro-furan-3-yl)propionamide 53a (1.28g, 2.5mmol), methanol (140ml) ethyl acetate (60ml) and 10% palladium on carbon (1.4g) was stirred under an atmosphere of hydrogen. After 2.5h more catalyst (300mg) was added and hydrogenation continued for 1h. The mixture was filtered through Celite™ and then refiltered through 0.2μM nylon filter

- 194 -

and concentrated. The residual oil triturated with a mixture of methanol and ether to afford 916mg (87%) of colorless crystals: mp. 198-200°C; $[\alpha]_D^{25}$ -120° (0.1, CH₃OH); IR (KBr) 3330, 1794, 1688, 1644, 1583, 1556, 1515, 1427; ¹H NMR (CD₃OD) δ 8.28 (1H, d), 7.35 (1H, d), 7.20 (5H, m), 6.36 (1H, t), 5.49 (1H, q), 4.59 (1H, t), 4.25 (1H, m), 2.98, 2.74 (2 x 2H, 2 x m), 2.59 (2H, m), 1.57 (3H, d). Anal. Calcd for C₂₁H₂₃N₃O₆ 0.75 H₂O: C, 59.08; H, 5.78; N, 9.84. Found: C 59.24; H, 5.96; N, 9.84. FAB M⁺ = 414 (M + 1), 297, 165, 91.

10 The following compounds were prepared in a similar manner:

15 3(S)-3-(6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl)acetyl amino-4-oxobutanoic acid, (54b; M), was isolated (59%) as colorless crystals: mp. 115°C (decomp);. IR (KBr) 3440, 3297, 1718, 1646, 1598, 1565, 1526, 1496, 1260; ¹H NMR (CD₃OD) 8.25 (1H, d, J=7.7), 7.25 (10H, m), 6.15 (1H, 2d, each J=7.7), 4.73 (2H, 2q), 4.59 (1H, m), 4.30 (1H, m), 3.95 (2H, s), 2.98 (2H, m), 2.75 (2H, m), 2.8-2.42 (2H, m). Anal. Calcd for C₂₇H₃₂N₃O₆. 0.7 H₂O: C, 64.58; H, 5.70; N, 8.37. Found: C, 64.51; H, 5.63; N, 8.38. MS FAB+ M⁺ = 490 (M + 1).

25 3(S)-3-(1,2-Dihydro-2-oxo-6-phenethyl-3-(3-phenyl-propionyl)amino-1-pyridyl)acetyl amino-4-oxobutanoic acid (54c), was isolated (46%) as a white solid: IR (KBr) 3375, 1694, 1643, 1586, 1561, 1515, 1377, 1254, 1188, 1070; ¹H NMR (CD₃OD) 8.18 (1H, d, J=7.8), 7.22 (10H, m), 6.15 (1H, d, J=7.8), 4.75 (2H, s), 4.58 (1H, m), 4.30 (1H, m), 3.01-2.28 (10H, m); MS FAB+ M⁺ = 504 (M + 1).

- 195 -

3(S) 3-(6-Butyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl)acetyl amino-4-oxobutanoic acid (54d), was isolated (90%) as colorless crystals: m.p. 120-5°C; IR (KBr) 3315, 1784, 1679, 1644, 1589, 1561, 1556, 1520, 1415, 1379, 1186; ¹H NMR (CD₃OD) δ 8.22 (1H, d, J=7.8), 7.24 (5H, m), 6.22 (1H, d, J=7.8), 4.80 (2H, m), 4.60 (1H, s), 4.28 (1H, m), 2.98 (2H, m), 2.72 (2H, m), 2.58 (4H, m), 1.48 (4H, m), 0.97 (3H, t, J=7.1). Anal. Calcd for C₂₄H₂₉N₃O₆ 0.5 H₂O: C, 62.06; H, 6.51; N, 9.05. Found: C, 62.08; H, 6.43; N, 9.01. MS FAB+ M⁺ = 456 (M + 1).

3(S) 3-(1,2-Dihydro-6-methyl-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl)acetyl amino-4-oxobutanoic acid (54e), was isolated (85%) as a colorless solid: mp. 129-138°C; IR (KBr) 327, 3294, 1710, 1695, 1682, 1554, 1525, 1379, 1272, 1240; ¹H NMR (CD₃OD) δ 8.19 (1H, d, J=7.6), 7.19 (5H, m), 6.21 (1H, d, J=7.6), 4.80 (2H, m), 4.59 (1H, m), 4.30 (1H, m), 2.98 (2H, m), 2.72 (2H, m), 2.80-2.40 (2H, m), 2.30 (3H, s). Anal. Calcd for C₂₁H₂₆N₃O₆. H₂O: C, 58.46; H, 5.84; N, 9.74. Found C: 58.82; H, 60.5; N, 9.42.

3(S) 3-(1,2-Dihydro-2-oxo-6-phenyl-3-(3-phenylpropionyl)amino-1-pyridyl)acetyl amino-4-oxobutanoic acid (54f), 73% as an off-white solid: m.p. 140°C (decomp). [α]_D²⁴ = -8.5° (c 0.1, MeOH). IR (KBr) 3302, 1796, 1726, 1679, 1643, 1590, 1560, 1516, 1490, 1449, 1420, 1398, 1376, 1231; ¹H NMR (CD₃OD) δ 8.36 (1H, d), 7.49-7.14 (10H, m), 6.27 (1H, dd), 4.54 (3H, m), 4.30 (1H, m), 3.0, 2.73 (2 x 2H, 2 x m), 2.7-2.29 (2H, m).

30 3(S) 3-(1,2-Dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl)acetyl amino-4-oxobutanoic acid (54g; G), was isolated (73%) as a foam: mp. 140-5°C (decomp); IR

- 196 -

(KBr) 3352, 3314, 1719, 1700, 1668, 1649, 1600, 1559,
1514, 1379, 1261; ^1H NMR (CD_3OD) δ 8.32 (1H, d, $J=7.5$),
7.19 (6H, m), 6.34 (1H, t), 5.1-4.6 (3H, m), 4.32 (1H,
m), 2.7 (6H, m). Anal. Calcd for $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_6$. 0.6 H_2O : C,
5 58.50, H, 5.45, N, 10.24. Found: C, 58.43, H, 5.35, N.
9.85. MS FAB+ $\text{M}^+ = 400$ ($\text{M} + 1$).

10 $3(S)$, $\text{N}(2(R,S))$ 3-(2-(6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl)propionylamino)-4-oxobutanoic acid (54h), was obtained (69%) as a colorless foam: m.p. 120°C; $[\alpha]_D^{20} -16.0^\circ$ (c, 0.11, CH_2Cl_2). IR (KBr) 3315, 1783, 1727, 1666, 1644, 1599, 1564, 1517, 1454, 1379; ^1H NMR (CD_3OD) δ 8.23 (1H, m), 7.27 (10H, m), 6.28 (1H, m), 4.84 (1H, m), 4.53 (1H, m), 4.22 (1H, m), 4.10 (2H, m), 2.96 (2H, m), 2.72 (2H, m), 2.39 (2H, m), 1.21 (3H, m). Anal. Calcd for $\text{C}_{28}\text{H}_{29}\text{N}_3\text{O}_6$. 1.25 H_2O : C, 63.93, H, 6.03, N, 7.99. Found: C, 63.98, H, 5.85, N, 7.86. MS FAB (+) $\text{M}^+ = 504$ ($\text{M} + 1$).

20 $3(S)$ 3-(3-(2-Acetyl-L-tyrosinyl)amino-6-benzyl-1,2-dihydro-2-oxo-1-pyridyl)acetylamino-4-oxobutanoic acid (54i), was isolated (79%) as colorless crystals: mp. 193-6°C (decomp.); IR (KBr) 3284, 1644, 1599, 1565, 1519, 1455, 1429, 1407, 1375, 1267, 1251; ^1H NMR ($d_6\text{-DMSO}/\text{CDCl}_3$) δ 8.16 (1H, d, $J=7.7$), 7.26 (5H, m), 7.03 (2H, d, $J=8.4$), 6.61 (2H, d, $J=8.4$), 6.03 (1H, d, $J=7.7$), 4.58 (3H, m), 4.44 (1H, m), 4.13 (1H, m), 3.84 (2H, s), 3.07-2.30 (4H, m). Anal. Calcd for $\text{C}_{29}\text{H}_{30}\text{N}_4\text{O}_6$. 2 H_2O : C, 58.19; H, 5.72; N, 9.36. Found: C, 58.11; H, 5.63; N, 9.29. MS FAB+ $\text{M}^+ = 563$ ($\text{M} + 1$).

25 30 $3(S)$ 3-(6-Benzyl-1,2-dihydro-2-oxo-3-(2-phenylethane-sulphonyl)amino-1-pyridyl)acetylamino-4-oxobutanoic acid (54j), was isolated (85%) as a colorless solid:

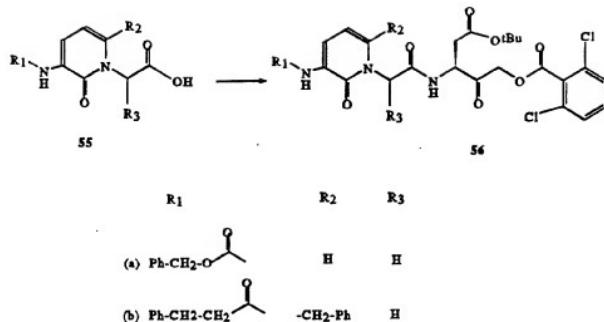
- 197 -

mp. 102-5°C; $[\alpha]_D^{23} -9.9^\circ$ (c 0.1, MeOH); IR (KBr) 3452, 3328, 3155, 1719, 1645, 1594, 1567, 1453, 1425, 1357, 1307, 1225, 1148, 1132; ^1H NMR (CD_3OD) δ 7.52 (1H, d, $J=7.6$), 7.33 (10H, m), 6.12 (1H, d, $J=7.6$), 4.73 (2H, m), 4.58 (1H, d, $J=3.7$), 4.34 (1H, m), 3.97 (2H, s), 3.29 (2H, m), 3.08 (2H, m), 2.75-2.37 (2H, m).
5 Anal. Calcd for $\text{C}_{26}\text{H}_{27}\text{N}_3\text{O}_4\text{S}$. 1.7H₂O: C, 56.14; H, 5.51; N, 7.55. Found: C, 56.20; H, 5.49; N, 7.29. MS FAB+ M⁺ = 526 (M + 1).

10 3(S)-3-(6-Benzyl-1,2-dihydro-2-oxo-3-(2-phenylethoxy)carbonylamino-1-pyridyl)acetylarnino-4-oxobutanoic acid (54k), was isolated (54%) as an off-white solid: mp. 84-86°C; IR (KBr) 3373-3310, 1787, 1726, 1691, 1649, 1599, 1567, 1517, 1367, 1215; ^1H NMR (CD_3OD) δ 7.93 (1H, bd, $J=7.4$), 7.37-7.18 (10H, m), 6.15 (1H, d, $J=7.4$), 4.77 (1H, d, $J=3.7$), 4.67 and 4.58 (2H, 2m), 4.35 (2H, t, $J=6.9$), 4.35 (1H, m), 3.94 (2H, s), 2.98 (2H, t, $J=6.9$), 2.76-2.39 (2H, m).

15 3(S)-3-(6-Benzyl-1,2-dihydro-2-oxo-3-(4-phenylbutyryl)carbonylamino-1-pyridyl)acetylarnino-4-oxobutanoic acid (54l), was isolated (50%) as a white solid: mp. 89-93°C; IR (KBr) 3369-3302, 1678, 1645, 1594, 1565, 1517, 1379, 1258; ^1H NMR (d_4 -methanol) δ 8.25 (1H, d, $J=7.6$), 7.37-7.18 (10H, m), 6.15 (1H, d, $J=7.4$), 4.74 (2H, m), 4.60 (1H, m), 4.30 (1H, m), 3.97 (2H, s), 2.76-2.37 (2H, m), 2.67 (2H, t), 2.45 (2H, t), 1.98 (2H, m). Anal. Calcd for $\text{C}_{26}\text{H}_{29}\text{N}_3\text{O}_6$. 1.5H₂O: C, 63.39; H, 6.08; N, 7.92. Found C: 63.69; H, 5.74; N, 7.83.

- 198 -

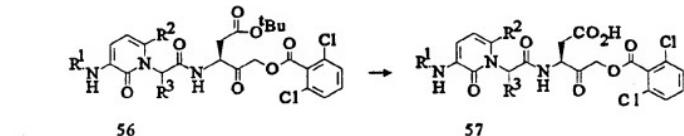


t-Butyl N-2-(3-benzyloxycarbonylamino-1,2-dihydro-2-oxo-1-pyridyl)acetyl-3-amino-5-(2,6-dichlorobenzoyloxy)-4-oxo-pentanoate (56a). The acetic acid (55a) (WO 93 21213) in THF (2ml) was stirred at room temperature and treated with 1-hydroxybenzotriazole (60mg, 0.448mmol) and dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (47mg, 0.246mmol). After 5 mins water (2 drops) was added and stirring continued for 20 minutes. Bis(triphenylphosphine) palladium II chloride (6mg) was added followed by a solution of t-butyl 3-(allyloxycarbonylamino)-4-oxo-5-(2,6-dichlorobenzoyl-oxy)pentanoate (WO 93 16710) (103mg, 0.224mmol) in THF (1ml). Tributyltin hydride (0.09ml, 0.336mmol) was added dropwise over 1 hour at room temperature. The mixture was stirred for a further 3 hours and poured onto ethyl acetate, washed with 1M HCl, aqueous NaHCO₃, brine, dried over MgSO₄, and concentrated in vacuo. The residue was triturated with pentane and the supernatant discarded. The remaining solid was purified by flash chromatography (50% ethyl acetate/hexane) to afford the title compound 92mg (63%).

- 199 -

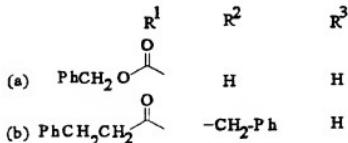
as a colorless oil: $[\alpha]_D^{26} -29.6^\circ$ (c 1.1, CH_2Cl_2); IR (film) 3377, 3365, 3332, 3312, 1733, 1691, 1650, 1599, 1515, 1366, 1261, 1153, 1068, 747; ^1H NMR (CDCl_3) δ 8.09 (1H, d, $J = 6.8$), 7.84 (1H, s), 7.58 (1H, d, $J = 8.3$), 7.33 (8H, m), 7.02 (1H, dd, $J = 6.9, 1.7$), 6.33 (1H, t, $J = 7.2$), 5.20 (2H, s), 5.12 (2H, m), 4.89 (1H, dt), 4.65 (2H, m), 2.80 (2H, m), 1.38 (9H, s).

t-Butyl N-2-(6-benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl)acetyl-3-amino-5-(2,6-dichlorobenzylxy)-4-oxo-pentanoate (56b), was prepared 10 by the method described for (56a) which afforded the title compound (66%) as a colorless oil: IR (film) 3364, 3313, 1738, 1688, 1648, 1600, 1566, 1514, 1433, 1369, 1254, 1152; ^1H NMR (CDCl_3) δ 8.40 (1H, d, $J = 7.6$), 8.30 (1H, s), 7.28 (13H, m), 6.20 (1H, d, $J = 7.6$), 5.12 (2H, q), 4.86 (1H, m), 4.65 (2H, q), 4.06 (2H, s), 3.07-2.61 (6H, m), 1.39 (9H, s).



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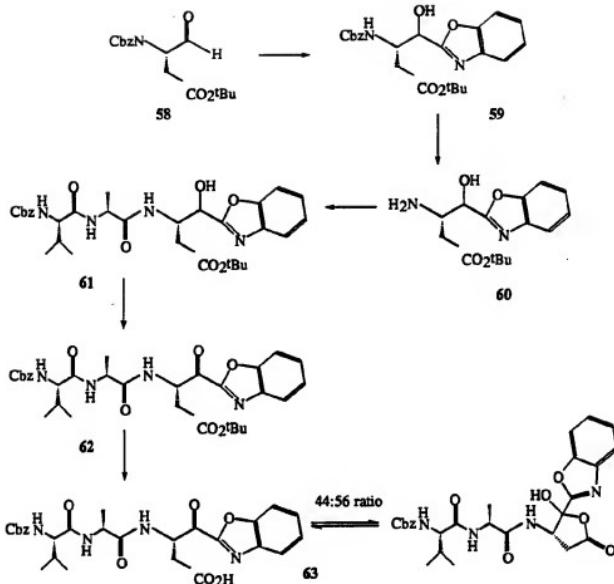


- 200 -

N-2-(3-Benzylloxycarbonylamino-1,2-dihydro-2-oxo-1-pyridyl)acetyl-3-amino-5-(2,6-dichlorobenzoyloxy)-4-oxo-pentanoic acid (57a; Q). The ester (56a) (210mg, 0.356mmol) in dichloromethane (0.5ml) was cooled to 0°C and treated with trifluoroacetic acid (0.5ml), stirred and warmed to 20°C over 30 minutes. The solution was evaporated to dryness under reduced pressure, redissolved in dichloromethane and concentrated (x3). The residue was triturated with ethyl acetate and diluted with ether to afford the title compound 162mg (85%) as a colorless solid: m.p. 165-8°C (decomposition); $[\alpha]_D^{23} -38.8^\circ$ (c 0.1, CH₃OH); IR (KBr) 3332, 3275, 1723, 1658, 1649, 1597, 1581, 1562, 1526, 1432, 1385, 1258, 1218, 1206; ¹H NMR (d₆-DMSO) δ 8.96 (1H, d, J = 7.3), 8.34 (1H, s), 7.85 (1H, dd, J = 7.3), 7.58 (3H, m), 7.35 (5H, m), 6.29 (1H, t, J = 7.3), 5.26 (2H, m), 5.15 (2H, s), 4.69 (3H, m), 2.75 (2H, m). Anal. Calcd. C₂₇H₂₃N₃O₈Cl₂: C, 53.66; H, 3.84; N, 6.95. Found: C, 53.36; H, 3.90; N, 6.81. M.S. (+ FAB); 604 (M⁺ + 1), 285, 241, 195, 173, 149, 91.

N-2-(6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl)acetyl-3-amino-5-(2,6-dichlorobenzoyloxy)-4-oxo-pentanoic acid (57b; P), was prepared by the method described for 57a which afforded the title compound (78%) as colorless crystals: m.p. 116-120°C (decomposition); $[\alpha]_D^{26} -41.1^\circ$ (c 0.1, CH₃OH); IR (KBr) 3299, 1739, 1715, 1689, 1666, 1645, 1598, 1563, 1518, 1432, 1209, 1151; ¹H NMR (d₆-DMSO) δ 9.24 (1H, s), 8.88 (1H, d, J = 7.6), 8.18 (1H, d, J = 7.7), 7.60 (3H, m), 7.26 (10H, m), 6.06 (1H, d, J = 7.7), 5.23 (2H, ABq), 4.69 (3H, m), 3.93 (2H, s), 2.78 (6H, m). Anal. Calcd. for C₃₅H₃₁N₃O₈Cl₂. H₂O: C, 59.16; H, 4.68; N, 5.91. Found: C, 59.38; H, 4.53; N, 5.84. M.S. (+ FAB); 694, (Cl=35, 37), (M⁺ + 1); 692 (Cl=35, 35), (M⁺ + 1).

- 201 -



(3S, 4R,S) t-Butyl N-(benzyloxycarbonyl)-3-amino-4-(2-benzoxazolyl)-4-hydroxy-butanoate (59). To a stirred solution of benzoxazole (250.2mg, 2.1mmol) in anhydrous THF (10.5ml) at -78°C under N₂ was added 2.3M n-butyl lithium in hexanes (0.96ml, 2.2mmol) dropwise. After stirring at -78°C for 20min, dry MgBr₂OEt₂ (594.0mg, 2.3mmol) was added as a solid. The resulting heterogeneous mixture was warmed to -45°C and stirred for 15min. The reaction mixture was then recooled to -78°C and a solution of aldehyde 58 (Graybill et al., Int. J. Peptide Protein Res., 44, pp. 173-182 (1993)) (644.6mg, 2.1mmol) in THF (10.5ml) was added dropwise:

- 202 -

The reaction was stirred at -78°C for 30min, warmed to 0°C for 1h, and then stirred at room temperature for 16h. The reaction was quenched with 5% sodium bicarbonate (2.0ml) and the THF was removed in vacuo.

5 The resulting aqueous residue was extracted four times with methylene chloride. The combined extracts were washed with brine, dried (MgSO_4), filtered and reduced in vacuo to give 880.0mg of crude product. Flash chromatography (45:55 ethyl acetate/hexane) afforded
10 567.2mg (63%) of the title compound, an oil, as a mixture of diastereoisomers at C-4. IR (film) 3324, 2976, 1726, 1517, 1455, 1368, 1243, 1159, 1048, 747; ^1H NMR (CDCl_3) δ 7.71-7.64 (1H, m), 7.52-7.48 (1H, m), 7.37-7.20 (7H, m), 5.91 (1H, brd, J = 9.0), 5.79 (1H, d, J = 9.0), 5.41-4.78 (4H, m), 4.75-4.54 (1H, m), 2.91-2.51 (2H, m), 1.42 (9H, s), 1.37 (9H, s).

15 (3S, 4R,S) t-Butyl 3-amino-4-(2-benzoxazolyl)-4-hydroxybutanoate (60). A solution of the ester 59 (189.0mg, 0.44mmol) in ethanol (5.0ml) was treated with 20 10% Palladium on carbon (20.5mg) and stirred under an atmosphere of H_2 for 21h. The mixture was filtered through Celite®, and the solvent was evaporated to afford 125.0mg (98%) of crude amine 60 as an oil. This was used without further purification. ^1H NMR (CDCl_3)
25 δ 7.73-7.64 (1H, m), 7.51-7.42 (1H, m), 7.35-7.22 (2H, m), 6.48 (3H, brs), 5.58 (1H, d, J = 3.0), 5.27 (1H, d, J = 6.5), 4.23-4.05 (1H, m), 2.92-2.63 (2H, m), 1.36 (9H, s), 1.33 (9H, s).

30 (3S, 4R,S) t-Butyl N-(N-benzyloxycarbonyl-(S)-valinyl-(S)-alaninyl)-3-amino-4-(2-benzoxazolyl)-4-hydroxybutanoate (61). A solution of the amine 60 (261.4mg, 0.89mmol), Z-Val-Ala-OH (286.9mg, 0.89mmol) (prepared by standard peptide synthetic procedures) and

- 203 -

hydroxybenzotriazole (120.3mg, 0.89mmol) in DMF (3.0ml) at 0°C was treated with 1-ethyl-3-[3-(dimethylamino) propyl]carbodiimide hydrochloride (179.2mg, 0.93mmol). The reaction was warmed to room temperature and stirred 5 for 16h. The reaction was diluted with ethyl acetate and washed twice with 1M sodium hydrogensulphate, twice with saturated sodium bicarbonate, then water, and brine. The organic layer was dried (MgSO_4), filtered and reduced *in vacuo* to afford 494.8mg of crude 10 product. Flash chromatography (95:5 methylene chloride/methanol) gave 480.9mg (91%) of the title compound as a yellow solid: mp. 81-83°C; IR (KBr) 3312, 2974, 1723, 1709, 1529, 1455, 1368, 1243, 1156, 747; ^1H NMR (CDCl_3) δ 7.79 (0.5H, d, J = 8.0), 7.73-7.20 (9.5H, m), 6.15 (1H, t, J = 8.5), 5.74 (0.5H, brd, J = 5.5), 5.45 (1H, brd, J = 7.5), 5.28-5.20 (0.5H, m), 4.82-4.11 (3.5H, m), 4.78-4.55 (1H, m), 4.40-4.22 (1H, m), 2.95-2.51 (2H, m), 2.12-1.95 (1H, m), 1.45-1.32 (12H, m), 1.11-0.81 (6H, m); ^{13}C NMR (CDCl_3) δ 173.14, 172.94, 171.82, 171.03, 170.78, 165.98, 165.45, 157.29, 157.17, 151.23, 151.10, 140.92, 140.82, 136.83, 136.79, 128.91, 128.52, 125.75, 124.97, 120.60, 120.40, 111.38, 81.82, 81.68, 70.27, 68.97, 67.44, 60.43, 50.74, 50.55, 49.18, 49.07, 36.87, 36.57, 32.37, 28.51, 19.88, 19.80, 25 18.53. Anal. Calcd. for $\text{C}_{31}\text{H}_{40}\text{N}_4\text{O}_6$. H_2O : C, 60.57; H, 6.89; N, 9.11. Found: C, 60.84; H, 6.64; N, 9.09. M.S. (+ FAB); 597 ($M^+ + 1$); 541, 91.

(3S) *t*-Butyl N-(*N*-benzyloxycarbonyl-*(S*)-valinyl-*(S*)-alaninyl)-3-amino-4-(2-benzoxazolyl)-4-oxobutanoate 30 (62). The alcohol 61 (100.3mg, 0.17mmol) was dissolved in methylene chloride (2.0ml) and Dess-Martin reagent (142.6mg, 0.34mmol) was added (Ireland et al., *J. Org. Chem.*, 58, p. 2899 (1993); Dess et al., *J. Org. Chem.*, 48, pp. 4155-4156 (1983)). The resulting mixture was

- 204 -

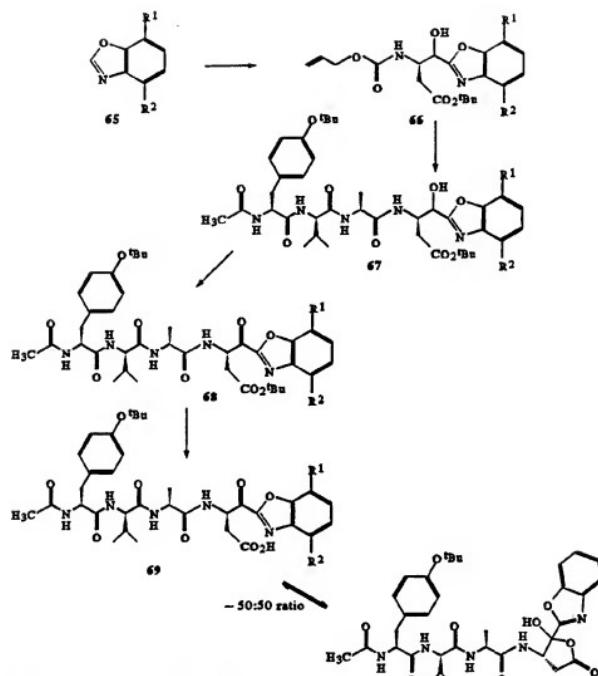
stirred for 22min and then partitioned between
saturated sodium thiosulphate: saturated sodium
bicarbonate (1:1, 10ml), and ethyl acetate (10ml). The
resulting organic phase was washed with saturated
5 sodium thiosulphate, saturated sodium bicarbonate
(1:1), saturated sodium bicarbonate, and brine. The
organic phase was dried ($MgSO_4$), filtered and reduced *in*
vacuo to give 111.3mg of crude product. Flash
chromatography (95:5 methylene chloride/methanol)
10 afforded 97.3mg (96%) of the title compound as an oil:
 $[\alpha]_D^{23} -11.74^\circ$ (c 0.95, CH_2Cl_2); IR (CH_2Cl_2) 3419, 2974,
1721, 1677, 1501, 1369, 1221, 1156; 1H NMR ($CDCl_3$) δ
7.89-7.84 (1H, m), 7.73-7.22 (10H, m), 5.98 (1H, d, J =
9.0), 5.72 (1H, m), 5.10 (2H, q, J = 12.5), 4.73 (2H,
15 m), 4.20 (1H, dd, J = 7.0, 8.5), 3.30 (1H, dd, J = 5.0,
16.5), 3.03 (1H, dd, J = 5.5, 16.5), 2.18-1.97 (1H, m),
1.39 (3H, d, J = 7.0), 1.34 (9H, s), 0.93 (3H, d, J =
6.0), 0.90 (3H, d, J = 6.0), ^{13}C NMR ($CDCl_3$) δ 186.46,
172.73, 171.90, 170.13, 157.17, 156.28, 151.16, 140.99,
20 136.99, 129.39, 129.08, 128.66, 128.59, 126.49, 123.06,
112.55, 82.73, 67.60, 60.84, 53.75, 49.41, 38.58,
32.05, 28.52, 19.85, 19.32, 18.51. M.S. (+ FAB); 595
($M^+ + 1$); 539, 91.

(3*S*) N-(*N*-Benzylloxycarbonyl-*(S*)-valinyl-*(S*)-alaninyl)-
25 3-amino-4-(2-benzoxazolyl)-4-oxobutanoate (63; Q). A
solution of the ester 62 (95.0mg, 0.16mmol) in a 1:1
mixture of methylene chloride and trifluoroacetic acid
(10.0ml) was stirred for 1h under a dry atmosphere of
N₂. The solution was then reduced *in vacuo*, taken up in
ether and reduced again. This process was repeated six
times to afford the crude product as an off white
solid. Flash chromatography (95:5 methylene
chloride/methanol) gave 60.0mg (69%) of the title
compound as a white solid. The product existed as a

- 205 -

mixture of three isomers in CD₃OD, consisting of the ketone form (one isomer, c 44%), and its acycloxy ketal form (two isomers at C-4, c. 56%): m.p. 156-159°C [α]_D²⁶
-45.6° (c 0.13, methanol); IR (KBr) 3440, 2967, 1713,
5 1703, 1638, 1531, 1427; ¹H NMR (CD₃OD) δ 7.93-7.24 (9H,
m), 5.59 (1H, brt), 5.16-5.00 (2H, m), 5.0-4.78 (1H,
m), 4.50-4.22 (1H, m), 3.95-3.81 (1H, m), 3.11 (2H, d,
J = 6.5), 3.05-2.92 (1H, m), 2.70-2.39 (1H, m), 2.08-
1.89 (1H, m), 1.19-0.78 (9H, m). Anal. Calcd. for
10 C₂₇H₃₀N₄O₈. 0.5H₂O: C, 59.22; H, 5.71; N, 10.23. Found:
C, 59.48, H, 5.36, N, 10.17. M.S. (+ FAB); 539 (M⁺ +
1), 91.

- 206 -

(a) $R^1 = OCH_3$, $R^2 = H$ (b) $R^1 = H$, $R^2 = OCH_3$

7-Methoxybenzoxazole (65a). A mixture of 2-nitro-6-methoxyphenol (2.62g, 15.5mmol) (EP 333176) and 10% Palladium on carbon (130mg) in ethanol (50.0ml) was stirred under an atmosphere of H_2 for 75min. The mixture was filtered through Celite® then immediately treated with *p*-toluenesulphonic acid (32.0mg) and triethylorthoformate (6.45ml, 38.8mmol) then heated under reflux under an atmosphere of N_2 . After 20h *p*-

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- 207 -

toluenesulphonic acid (30.0mg) and triethylorthoformate (6.45ml, 38.8mmol) were added. After a total of 44h heating, the reaction was allowed to cool and reduced in vacuo. The resulting residue was purified by flash chromatography (25:75 ethyl acetate/hexane) to give 1.97g (85%) of the title compound as a yellow solid: m.p. 28-31°C; IR (film) 1629, 1497, 1434, 1285, 1097; ¹H NMR (CDCl₃) δ 8.09 (1H, s), 7.40 (1H, d, J = 8.0), 7.28 (1H, t, J = 8.0), 6.89 (1H, d, J = 8.0), 4.02 (3H, s); ¹³C NMR (CDCl₃) δ 152.84, 145.82, 142.50, 139.99, 125.75, 113.42, 108.80, 56.97. Anal. Calcd. for C₈H₇N₁O₂. 0.1H₂O: C, 63.65; H, 4.81; N, 9.29. Found: C, 63.43, H, 4.88, N, 9.05. M.S. (+ FAB); 150 (M⁺ + 1).

4-Methoxybenzoxazole (65b). To a suspension of 4-hydroxybenzoxazole (2.00g, 14.8mmol) (Musser et al., J. Med. Chem., 30, pp. 62-67 (1987)) in acetone (80.0ml) was added dried K₂CO₃ (2.25g, 16.3mmol) followed by iodomethane (1.38ml, 22.2mmol). The reaction was heated under reflux under N₂ for 4.5h, then filtered and reduced in vacuo to afford the crude product. The resulting residue was purified by flash chromatography (25:75 ethyl acetate/hexane) to give 2.0g (91%) of the title compound as a white crystalline solid: m.p. 72-74°C; IR (KBr) 3089, 1619, 1610, 1503, 1496, 1322, 1275, 1090, 1071, 780, 741; ¹H NMR (CDCl₃) δ 8.02 (1H, s), 7.32 (1H, t, J = 8.0), 7.18 (1H, d, J = 8.0), 6.81 (1H, d, J = 8.0), 4.04 (3H, s). Anal. Calcd. for C₈H₇NO₂: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.40; H, 4.84; N, 9.31; m/z (EI) 149 (M⁺ + 1, 100%).

(3*S*, 4*R*, *S*) *t*-Butyl N-(allyloxycarbonyl)-3-amino-4-hydroxy-4-(2-(7-methoxybenzoxazolyl))butanoate (66a). To a stirred solution of 7-methoxybenzoxazole 65a (548.6mg, 3.68mmol) in anhydrous THF (18.5ml) at -78°C

- 208 -

under N₂ was added 1.56M *n*-butyl lithium in hexanes (2.47ml, 3.86mmol) dropwise, to produce a yellow colored solution. After stirring at -78°C for 20 min, dry MgBr₂OEt₂ (1.045g, 4.05mmol) was added as a solid.

5 The resulting heterogeneous mixture was warmed to -45°C and stirred for 15min. The reaction mixture was then recooled to -78°C and a solution of (*S*)-Alloc-Asp(*t*-Bu)H^{1b} (946.4mg, 3.68mmol) in THF (18.5ml) was added dropwise. The reaction was stirred at -78°C for 30min,

10 warmed to 0°C and stirred for 1h. The resulting homogeneous reaction was warmed to room temperature and stirred for 16h. The reaction was quenched with 5% sodium bicarbonate (3.5ml) then THF was removed in vacuo. The resulting aqueous residue was extracted with methylene chloride (x6). The combined extracts were washed with brine, dried (MgSO₄), filtered and reduced in vacuo to give 1.8g of crude product. Flash chromatography (40:60 ethyl acetate/hexane) gave 1.21g

15 (81%) of the title compound, an oil, as a mixture of diastereoisomers at C-4: IR (CH₂Cl₂) 3425, 2983, 1725, 1504, 1290, 1157, 1101; ¹H NMR (CDCl₃) δ 7.35-7.19 (2H, m), 6.89-6.81 (1H, m), 6.00-5.57 (2H, m), 5.32-5.05 (3H, m), 4.68-4.35 (3H, m), 4.01 (3H, s), 2.86-2.59 (2H, m), 1.45 (9H, s), 1.41 (9H, s); ¹³C NMR (CDCl₃) δ

20 171.18, 171.09, 165.80, 165.30, 156.71, 156.60, 145.65, 142.76, 142.71, 140.82, 140.72, 133.23, 125.81, 125.72, 118.41, 118.21, 113.07, 112.87, 108.95, 82.16, 70.28, 69.98, 66.52, 66.39, 57.03, 52.57, 52.29, 37.83, 36.86, 28.65. Anal. Calcd. for C₂₀H₂₆N₂O₄. 0.6H₂O: C, 57.57; H, 6.57; N, 6.72. Found: C, 57.49, H, 6.34, N, 6.60. M.S. (+ FAB); 407 (M' + 1); 351, 307, 154.

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(*3S, 4R,S*) *t*-Butyl N-(allyloxycarbonyl)-3-amino-4-hydroxy-4-(2-(4-methoxybenzoxazolyl)butanoate (66b), was prepared according to the method described for 66a

- 209 -

which afforded 1.29g (26%, 68% based on recovered starting material) of the title compound as an oil and as a mixture of diastereoisomers at C-4: IR (CH₂Cl₂) 3400, 1725, 1625, 1505, 1369, 1354, 1281, 1263, 1226, 1158, 1092, 1048; ¹H NMR (CDCl₃) δ 7.34-7.24 (1H, m), 7.16 (1H, d, J = 8.2), 6.79 (1H, d, J = 7.9), 6.00-5.50 (2H, m), 5.30-5.05 (3H, m), 4.70-4.35 (4H, m), 4.02 (3H, s), 2.90-2.45 (2H, m), 1.45-1.41 (9H, 2 x s). Anal. Calcd. for C₂₀H₂₂N₂O₇. 0.4H₂O: C, 58.07; H, 6.53; N, 6.77. Found: C, 58.09; H, 6.41; N, 6.63. M.S. (+ FAB); 407 (M⁺ + 1, 88%); 351 (100).

(3*S*, 4*R,S*) t-Butyl N-(N-acetyl-(S)-(O-tert-butyl-tyrosinyl)-(S)-valinyl-(S)-alaninyl)-3-amino-4-hydroxy-4-(2-(7-methoxybenzoxazolyl))butanoate (67a). To a stirred solution of the benzoxazole 66a (481.9mg, 1.19mmol) and Ac-Tyr(^tBu)-Val-Ala-OH (586.3mg, 1.30mmol) in methylene chloride (3.5ml) and DMF (3.5ml) was added bis(triphenylphosphine) palladium (II) chloride (18.0mg), followed by tributyltinhydride (0.80ml, 2.96mmol) dropwise. Hydroxybenzotriazole (320.4mg, 2.37mmol) was added and the mixture cooled to 0°C. 1-Ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (278.2mg, 1.42mmol) was added and the mixture was allowed to warm to room temperature and stirred for 16.5h. The reaction was diluted with ethyl acetate and washed twice with 1M sodium hydrogensulphate, twice with saturated sodium bicarbonate, water, and brine. The organic layer was dried (MgSO₄), filtered and reduced in vacuo to yield 2.0g of crude product. Flash chromatography (95:5 methylene chloride/methanol) gave 844.0mg (94%) of the title compound as a white solid: m.p. 205°C; IR (KBr) 3399, 3304, 2977, 1729, 1643, 1506, 1367, 1290, 1161; ¹H NMR (d₆-DMSO) δ 8.24-7.78 (4H, m), 7.43-7.32 (2H, m),

- 210 -

7.23 (2H, d, $J = 8.5$), 7.16-7.07 (1H, m), 6.93 (2H, d, $J = 8.5$), 6.52, 6.40 (1H, 2 x d, $J = 5.5$, $J = 5.0$), 5.03, 4.78-4.49, 4.45-4.16 (5H, brt, 2 x m), 4.05, 4.04 (3H, 2 x s), 3.08-2.35 (14H, m), 2.11-1.89 (1H, m),
5 1.83 (3H, s), 1.49-1.32, 1.15, 1.0-0.81 (27H, s, 2 x m, $J = 7.0$); ^{13}C NMR (d_6 -DMSO) δ 175.55, 175.18, 173.88, 173.75, 173.05, 169.23, 157.28, 148.55, 146.16, 143.21, 136.63, 133.55, 128.87, 127.17, 115.78, 111.92, 84.02, 81.50, 71.40, 61.15, 60.05, 57.79, 53.39, 51.62, 43.76,
10 40.52, 34.58, 32.52, 31.60, 26.35, 23.11, 22.71, 21.76.
Anal. Calcd. for $\text{C}_{39}\text{H}_{55}\text{N}_5\text{O}_{10}$. 0.5H₂O: C, 61.40; H, 7.40; N, 9.18. Found: C, 61.43; H, 7.31; N, 9.07. M.S. (+ FAB); 754 ($M^+ + 1$); 698, 338, 267.

(3*S*, 4*R*,*S*) t-Butyl N-(N-acetyl-(S)-(O-tert-butyl-tyrosinyl)-(S)-valinyl-(S)-alaninyl)-3-amino-4-hydroxy-4-(2-(4-methoxybenzoxazolyl))butanoate (67b), was prepared according to the method described for 67a which afforded 1.05g (94%) of the title compound as a fine white powder: m.p. 210-213°C (dec); IR (KBr) 3284, 2977, 1736, 1691, 1632, 1536, 1505, 1452, 1392, 1367, 1258, 1236, 1161, 1091; ^1H NMR (d_6 -DMSO) δ 8.20-7.75 (4H, m), 7.40-7.10 (4H, m), 7.00-6.80 (3H, m), 6.45, 6.34 (1H, 2 x d, $J = 5.3$, $J = 5.0$), 5.00-4.10 (5H, m), 4.00, 3.99 (3H, 2 x s), 3.00-2.25 (4H, m), 1.95 (1H, m), 1.78 (3H, s), 1.39-0.80 (27H, m). Anal. Calcd. for $\text{C}_{39}\text{H}_{55}\text{N}_5\text{O}_{10}$. 0.5H₂O: C, 61.40; H, 7.40; N, 9.18. Found: C, 61.58; H, 7.38; N, 8.91. M.S. (+ FAB); 754 ($M^+ + 1$, 30%); 72 (100).

(3*S*) t-Butyl N-(N-acetyl-(S)-(O-tert-butyl-tyrosinyl)-(S)-valinyl-(S)-alaninyl)-3-amino-4-(2-(7-methoxybenzoxazolyl))-4-oxobutanoate (68a). The Dess-Martin reagent (1.082g, 2.55mmol) (Ireland et al., J. Org. Chem., 58, p. 2899 (1993); Dess et al., J. Org.

- 211 -

Chem., 48, pp. 4155-4156 (1983)) was added to a stirred suspension of the alcohol 67a (641.0mg, 0.85mmol) in methylene chloride (46.0ml). The resulting mixture was stirred for 1h before being partitioned between
5 saturated sodium thiosulphate: saturated sodium bicarbonate (1:1, 86.0ml) and ethyl acetate (86.0ml). The resultant organic phase was washed in turn with saturated sodium thiosulphate: saturated sodium bicarbonate (1:1), saturated sodium bicarbonate, and brine. The organic phase was dried (MgSO_4), filtered and reduced in vacuo to give 660.0mg of crude product. Flash chromatography (94:6 methylene chloride/methanol) gave 636.0mg (100%) of the title compound as a white solid: m.p. 209°C; $[\alpha]^{24} -21.8^\circ$ (c 0.16, methanol); IR (KBr) 3395, 3294, 2977, 1722, 1641, 1535, 1505, 1161;
10 ^1H NMR (CDCl_3) δ 8.43-8.16 (1H, m), 7.97-7.62 (2H, m), 7.49-7.14 (3H, m), 7.08-6.95 (3H, m), 6.89-6.73 (2H, m), 5.81-5.68 (1H, m), 5.16-4.86 (2H, m), 4.53 (1H, brt), 4.03 (3H, s), 3.16-2.84 (4H, m), 2.11-1.84 (4H, m), 1.46-1.14 (21H, m), 0.92-0.78 (6H, m); ^{13}C NMR (CDCl₃) δ 186.28, 173.39, 171.90, 171.19, 171.03, 169.89, 156.43, 154.75, 146.32, 142.88, 140.98, 132.31, 130.54, 126.98, 124.73, 114.95, 111.42, 82.44, 78.71, 58.92, 57.20, 54.91, 53.47, 48.77, 39.43, 38.15, 32.79,
15 29.44, 28.60, 23.55, 20.27, 19.70, 19.34. M.S.
20 (+ FAB); 752 ($M^+ + 1$); 696, 336, 265.

(3S)-t-Butyl N-(N-acetyl-(S)-(O)-tert-butyl-tyrosinyl)-(S)-valinyl-(S)-alaninyl)-3-amino-4-(2-(4-methoxybenzoxazolyl))-4-oxobutanoate (68b), was
25 prepared according to the method described for the ketone 68a which afforded 420mg (55%) of the title compound as a white solid: m.p. 211-213°C (dec); $[\alpha]^{24} -23.9^\circ$ (c 0.82, methanol); IR (KBr) 3277, 3075, 1723, 1690, 1632, 1530, 1506, 1392, 1366, 1269, 1234, 1160,

- 212 -

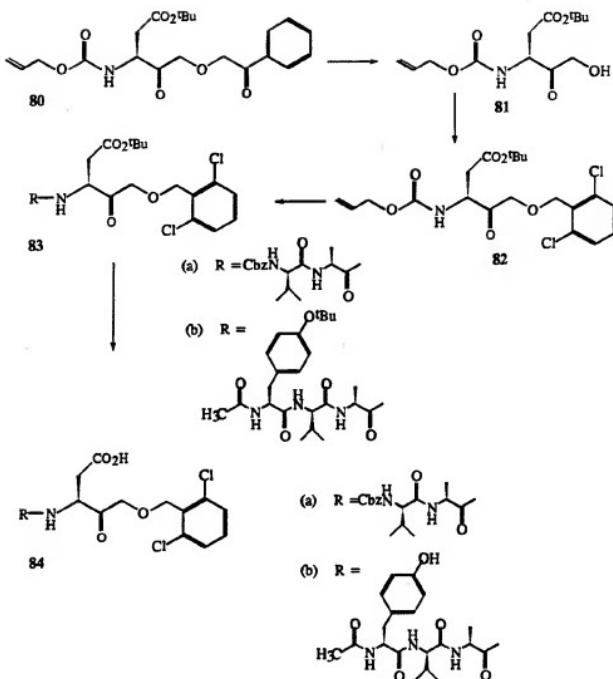
1094; ^1H NMR (CDCl_3) δ 8.15 (1H, brs), 7.7 (2H, brs),
7.46 (1H, t, J = 8.3), 7.24 (2H, d, J = 8.3), 7.10 (1H,
brs), 7.03 (2H, d, J = 8.3), 6.83 (3H, m), 5.74 (1H, q,
 J = 6.9), 5.00 (2H, m), 4.51 (1H, t, J = 7.0), 4.07
5 (3H, s), 3.20-2.95 (4H, m), 2.00 (4H, m), 1.42 (3H, d,
 J = 6.8), 1.35 (9H, s), 1.23 (9H, s), 0.86 (6H, d, J =
6.7). M.S. (+ FAB); 752 ($M^+ + 1$, 7%); 72 (100).

(3S)-N-(N-Acetyl-(S)-tyrosinyl-(S)-valinyl-(S)-alaninyl)-3-amino-4-(2-(7-methoxybenzoxazolyl))-4-oxobutanoate (69a; R). A solution of the ester 68a (600.0mg, 0.80mmol) in a 1:1 mixture of methylene chloride and trifluoroacetic acid (65.0ml) was stirred for 1h under a dry atmosphere of N_2 . The solution was then reduced in vacuo, taken up in ether and reduced again. This process was repeated six times to afford the crude product as an off white solid. Flash chromatography (gradient 95:5 to 80:20 methylene chloride/methanol) gave 420.8mg (83%) of the title compound as a hygroscopic white solid. The product existed as a mixture of three isomers in CD_3OD , consisting of the keto form (c 50%), and its acycloxy keto form (two isomers at C-4, c 50%): m.p. decomposes above 150°C; $[\alpha]_D^{24}$ -33.2° (c 0.17, methanol); IR (KBr) 3300, 1715, 1658, 1650, 1531, 1517, 1204; ^1H NMR (CD_3OD) δ 7.46-7.19 (2H, m), 7.16-6.91 (3H, m), 6.70-6.59 (2H, m), 5.62-5.49 (1H, m), 5.00-4.72 (1H, obscured m), 4.69-4.51 (1H, m), 4.49-4.08 (2H, m), 4.05-3.89 (3H, m), 3.16-2.47 (4H, m), 2.05-1.78 (4H, m), 1.41-1.11, 1.05-0.70 (9H, 2 x m). Anal. Calcd. for $\text{C}_{11}\text{H}_{17}\text{N}_5\text{O}_{10}$.
30 $3\text{H}_2\text{O}$: C, 53.67; H, 6.25; N, 10.10. Found: C, 53.76; H, 5.56; N, 10.28. M.S. (+ FAB); 640 ($M^+ + 1$); 435, 147.

- 213 -

(3*S*) *t*-Butyl N-(*N*-acetyl-(*S*)-tyrosinyl-(*S*)-valinyl-(*S*)-alaninyl)-3-amino-4-(2-(4-methoxybenzoxazolyl))-4-oxobutanoate (69b; **S**), was prepared according to the method described for the acid 69a which afforded the hygroscopic title compound 252mg (96%). The product existed as a mixture of three isomers in CD₃OD, consisting of the keto form, and its acycloxy ketal form (two isomers at C-4). The product existed as a single isomer in d-6 DMSO: m.p. 200-203°C (dec.); [α]_D²⁴ -38.0° (c 0.23, methanol); IR (KBr) 3289, 2968, 1718, 1713, 1658, 1634, 1548, 1517, 1506, 1461, 1453, 1393, 1369, 1268, 1228, 1174, 1092; ¹H NMR (d₆-DMSO) δ 9.20 (1H, brs), 8.71 (1H, d, J = 6.2), 8.10 (2H, m), 7.83 (1H, d, J = 8.7), 7.61 (1H, t, J = 8.2), 7.46 (1H, d, J = 8.2), 7.08 (3H, m), 6.65 (2H, d, J = 8.3), 5.50 (1H, q, J = 6.5), 4.50 (1H, m), 4.37 (1H, m), 4.20 (1H, m), 4.05 (3H, s), 3.09-2.77 (4H, m), 1.94 (1H, m), 1.79 (3H, s), 1.23 (3H, d, J = 7.0), 0.82 (6H, m). Anal. Calcd. for C₃₃H₃₇N₅O₁₀. 1.5H₂O: C, 55.85; H, 6.05; N, 10.51. Found: C, 55.21; H, 5.69; N, 10.13. M.S. (+ FAB); 640 (M' + 1, 22%); 107 (100).

- 214 -



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(3S) *t*-Butyl *N*-(allyloxycarbonyl)-*3*-amino-*4*-oxo-*5*-(1,2-dioxo-2-phenylethoxy)-pentanoate (80). Potassium fluoride (792mg, 13.6mmol) and then benzoyl formic acid (1.02g, 6.82mmol) were added to a stirred solution of *(3S)* *t*-butyl *N*-(allyloxycarbonyl)-*3*-amino-*5*-bromo-*4*-oxo-pentanoate (WO 93 16710) (2.17g, 6.20mmol) in dimethylformamide (30ml). The mixture was stirred for 140 mins, quenched with water (50ml) and extracted with

- 215 -

ethyl acetate (2 x 50ml). The combined organic extracts were washed with water (4 x 50ml) then brine (50ml). They were dried ($MgSO_4$) and concentrated to afford an oil which was purified by flash chromatography (20-45% ethyl acetate in hexane) to afford 2.44g (94%) of a colorless oil: $[\alpha]_D^{20} -35.0^\circ$ (c 1.41, CH_2Cl_2); IR (film) 3359, 2981, 2938, 1752, 1740, 1726, 1712, 1512, 1369, 1285, 1177, 1053, 991, 939, 688; 1H NMR ($CDCl_3$) δ 8.15 (2H, m), 7.66 (1H, m), 7.53 (2H, m), 5.90 (2H, m), 5.33 (2H, m), 5.31 (1H, d, $J = 16.9$), 5.18 (1H, d, $J = 16.9$), 4.63 (3H, m), 3.03 (1H, dd, $J = 17.3, 4.6$), 2.74 (1H, dd, $J = 17.3, 4.9$), 1.44 (9H, s). MS (C.I.) 420 ($M^+ + 1$ 20%); 364 (100).

(3S) t-Butyl N-(allyloxycarbonyl)-3-amino-5-hydroxy-4-oxo-pentanoate (81). A mixture of the ester 80 (2.40g, 5.71mmol), tetrahydrofuran (200ml) and 1M aqueous potassium bicarbonate (200ml) was vigorously stirred at room temperature for 18h. The layers were separated and the aqueous portion extracted with ethyl acetate (100ml). The combined organic extracts were washed with brine (100ml), dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (10-60% ethyl acetate in hexane) to afford 1.48g (90%) of pale yellow oil: $[\alpha]_D^{20} -5.9^\circ$ (c 1.06, CH_2Cl_2); IR (film) 3345, 2981, 2936, 1739, 1725, 1712, 1692, 1515, 1368, 1259, 1158, 1051; 1H NMR ($CDCl_3$) δ 5.92 (2H, m), 5.30 (2H, m), 4.36-4.69 (5H, m), 3.05 (1H, dd, $J = 17.4, 4.3$), 2.93 (1H, t), 2.70 (1H, dd, $J = 17.4, 4.9$), 1.43 (9H, s). Anal. Calcd for $C_{16}H_{21}N_3O_6$. 0.25H₂O: C, 53.51; H, 7.43; N, 4.80. Found: C, 53.61; H, 7.18; N, 4.71. MS (C.I.) 280 ($M^+ + 1$, 87%); 232 (100).

- 216 -

(3*S*) t-Butyl N-(allyloxycarbonyl)-3-amino-5-(2,6-dichlorophenyl-methoxy)-4-oxo-pentanoate (82). A stirred mixture of alcohol 81 (1.44g, 5.01mmol), 2,6-dichlorobenzyl iodide (Abraham et al., *J. Chem. Soc.*, pp. 1605-1607 (1936)) (4.31g, 15.0mmol), silver oxide (2.32g, 10.0mmol) and dichloromethane (25ml) was heated under reflux for 45h. The mixture was allowed to cool to room temperature then diluted with water (50ml) then extracted with ethyl acetate (50ml, 25ml). The organic layer was washed with water (50ml) then brine (50ml), dried (MgSO_4), and concentrated. The residue was purified by flash chromatography (10-100% ethyl acetate in hexane) to afford 1.65g (74%) of a colorless oil: $[\alpha]_D^{20} +8.8^\circ$ (*c* 1.13, CH_2Cl_2); IR (film) 3339, 2980, 2935, 1724, 1712, 1503, 1438, 1368, 1246, 1156, 1106, 770; ^1H NMR (CDCl_3) δ 7.33 (2H, m), 7.22 (1H, dd), 5.92 (2H, m), 5.28 (2H, m), 4.87 (2H, m), 4.67 (1H, m), 4.58 (2H, br d), 4.56 (1H, d, *J* = 16.9), 4.31 (1H, d, *J* = 16.9), 3.04 (1H, dd, *J* = 16.7, 4.5), 2.77 (1H, dd, *J* = 16.7, 4.9), 1.40 (9H, s). Anal. Calcd. for $\text{C}_{20}\text{H}_{25}\text{Cl}_2\text{N}_1\text{O}_6$. 0.25 H_2O : C, 53.28; H, 5.70; N, 3.11. Found: C, 53.15; H, 5.52; N, 2.98. M.S. (C.I.); 446 (M^+ , 27%); 390 (100).

(3*R,S*) t-Butyl N-[N-phenylmethyloxycarbonylvalaninyl-alaninyl]-3-amino-5-(2,6-dichlorophenylmethyloxy)-4-oxo-pentanoate (83a). 1-(3-Dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (379g, 1.98mmol) and 1-hydroxybenzotriazole (486mg, 3.60mmol) were added to a stirred solution of N-phenyl-methyloxycarbonylvalinylalanine (637mg, 1.98mmol) in tetrahydrofuran (40ml) and water (1ml). The mixture was stirred for 15mins and then the ether 82 (802mg, 1.80mmol) and bis(triphenylphosphine)palladium (II) chloride (ca 5mg) were added.

- 217 -

Tributyltin hydride (785mg, 725 l, 2.70mmol) was then added dropwise during 20mins and the resulting solution was stirred for 3.75h and then quenched with 1M hydrochloric acid (50ml). The mixture was extracted twice with ethyl acetate. The combined organic extracts were washed with 1M hydrochloric acid, twice with aqueous sodium bicarbonate, water and then brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (10-30% ethyl acetate - dichloromethane) to afford 941mg (79%) of pale yellow solid: m.p. 148-52°C; IR (KBr) 3287, 3070, 1730, 1691, 1641, 1536, 1369, 1289, 1247, 1156; 1H NMR ($CDCl_3$) δ 7.33 (8H, m), 7.23 (1H, dd), 6.61 (1H, br, d), 5.42 (1H, br, d), 5.11 (2H, s), 4.85 (3H, m), 4.50 (1H, m), 4.40 (1H, d, J = 16.9), 4.26 (1H, d, J = 16.9), 4.02 (1H, m), 2.99 (1H, dd, J = 16.8, 4.7), 2.73 (1H, dd, J = 16.8, 5.0), 2.09 (1H, m), 1.37 (12H, m), 0.96 (3H, d, J = 6.9), 0.91 (3H, d, J = 6.8). Anal. Calcd. for $C_{32}H_{41}Cl_2N_3O_8$. 0.25H₂O: C, 57.25; H, 6.23; Cl, 10.57; N, 5.26. Found: C, 57.18; H, 6.23; Cl, 10.58; N, 5.95. M.S. (+ FAB); 667 (M^+ 1, 1%); 666 (3), 159 (25), 91 (100).

(3*R*,*S*) t-Butyl N-[(N-acetyl-O-t-butyltyrosinyl)-valaninyl-alaninyl]-3-amino-5-(2,6-dichlorophenylmethoxy)-4-oxo-pentanoate (83b), was prepared by the method described for 83a to afford 554mg (64%) of colorless solid: m.p. 184-6°C; IR (KBr) 3282, 3075, 1736, 1690, 1633, 1536, 1508, 1366, 1236, 1161; 1H NMR (d_6 -DMSO) δ 8.49 (1H, d), 8.14 (1H, d), 8.08 (1H, d), 7.84 (1H, d), 7.43 (3H, m), 7.14 (2H, d), 6.83 (2H, d), 4.71 (2H, s), 4.51 (2H, m), 4.36 (2H, dd), 4.17 (2H, m), 2.93 (1H, m), 2.73 (1H, m), 1.94 (1H, m), 1.74 (3H, s), 1.37 (9H, s), 1.23 (12H, m),

- 218 -

0.83 (6H, m). M.S. (+ FAB); 793 (M^+ 1, 4%); 737 (5), 681 (1), 178 (40), 159 (45), 136 (100), 107 (40). M.S. (- FAB); 792 (20), 791 (40), 447 (100).

(*R,S*) N-[N-(Phenylmethoxy)carbonyl-valinyl-alaninyl]-5-amino-5-(2,6-dichlorophenylmethoxy)-4-oxo-pentanoic acid (84a; **V**). Trifluoroacetic acid (5ml) was added to a stirred solution of the ester 83a, (918mg, 1.38mmol) in dichloromethane (20ml). The mixture was stirred for 2.5h then evaporated to dryness. The residue was treated with ether (25ml) and evaporated to dryness. This procedure was repeated three times. The resulting product was triturated with ether (10ml) and then dried to afford 730mg (87%) of light brown powder: m.p. 156-60°C; IR (KBr) 3282, 2965, 1702, 1694, 1642, 1536, 1438, 1246, 1230; 1 H NMR (d_6 -DMSO) δ 8.48 (1H, d), 8.09 (1H, d), 7.47 (9H, m), 5.02 (2H, s), 4.70 (2H, s), 4.49 (1H, m), 4.37 (2H, dd), 4.27 (1H, m), 3.88 (1H, m), 2.75 (1H, dd), 2.54 (1H, dd), 1.96 (1H, m), 1.19 (3H, s), 0.84 (6H, m). Anal. Calcd. for $C_{26}H_{33}Cl_2N_3O_8$. 0.5H₂O: C, 54.27; H, 5.53; Cl, 11.45; N, 6.78. Found: C, 54.49; H, 5.39; Cl, 11.33; N, 6.73. M.S. (+ FAB); 610 (M^+ 1, 10%); 91 (100).

(*R,S*) N-[N-(Acetyl)tyrosinyl-valinyl-alaninyl]-3-amino-5-(2,6-dichlorophenylmethoxy)-4-oxo-pentanoic acid (84b; **W**), was obtained as a colorless powder (95%) by the method used for 84a. m.p. 165-8°C: IR (KBr) 3295, 2968, 1733, 1642, 1517, 1438, 1231, 1105; 1 H NMR (d_6 -DMSO) 9.2 (1H, br, s), 8.48 (1H, br, d), 8.14 (1H, br, d), 8.02 (1H, br, d), 7.81 (1H, br, d), 7.45 (3H, m), 7.02 (2H, d), 6.62 (2H, d), 4.70 (2H, s), 4.12-4.53 (3H, m), 3.60 (3H, m), 2.51-2.92 (4H, m), 1.96 (1H, m), 1.75 (3H, s), 1.21 (3H, d), 0.83 (6H, m). Anal. Calcd.

- 219 -

for $C_{11}H_{18}Cl_2N_4O_9$. H₂O: C, 53.22; H, 5.76; Cl, 10.14; N, 8.09. Found: C, 53.33; H, 5.54; Cl, 10.02; N, 7.85. M.S. (+ FAB); 682 (M⁺ 2, 30%); 681 (67), 158 (100). (- FAB); 680 (45), 679 (100).

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Example 6

We obtained inhibition constants (K_i) and IC₅₀ values for several compounds of this invention using enzyme assays with UV-visible substrate, fluorescent substrate, and cell assays as described in Example 2.

10 The following K_i and IC₅₀ values were determined for compounds 22e, 54b, 54j, 54k, 57b, 85, 86, 87, 88, 89, 90, 91, 92, 98, 102a-c, 106a-c, 108a-c, 114a, 114b, 115, 121, 125a, 125b, 126, 127, 128, 129, 130, 131, 132a, 132b, 133, 135a, 135b, 136, 137, 138, 139, 140, 141, 142, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, and 163 using the indicated assays. The structures of compounds 22e, 54b, 54j, 54k, and 57b are shown in Example 5. The other compound structures are shown in Example 7.

15

20

<u>Assay</u>			
	<u>Compound</u>	<u>UV-visible</u>	<u>Cell</u>
		K_i (μ M)	IC ₅₀ (μ M)
25	22e	0.19	>20
	54b		20
	54j		10
	54k		6.6
	57b		2.2
30	85	0.0035	9.8

- 220 -

	86	0.175	4.0
	87	7.2	35.0
	88	0.9	
	89	0.018	
5	90	0.42	6.2
	91	0.26	>25
	92	3.8	
	98	0.535	4.0
	102a		4.0
	102b	0.29	1.75
10	102c	0.68	
	106a	2.3	30.0
	106b	0.2	2.9
	106c	3.8	>30.0
	108a		17.5
	108b	0.4	25.0
15	108c	0.43	
	114a	0.12	3.8
	114b	3.7	
	115	0.345	6.0
	121	4.3	
	125a	0.39	>30.0
20	125b	0.060	0.30
	126	0.45	1.5
	127	0.39	8.0
	128	0.04	7.5
	129	0.59	25.0
	130		1.20
25	131	12.0	30.0
	132a	5.0	>30.0
	132b	12.5	
	133	50.0	>30.0
	135a	0.090	0.90
	135b	0.32	0.95

- 221 -

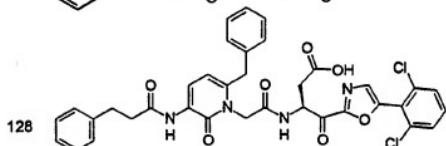
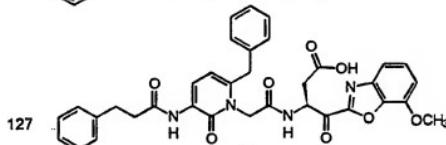
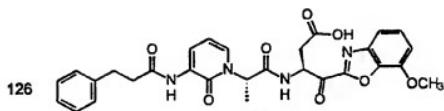
	136	1.0
	137	0.25
	138	0.375
	139	2.0
5	140	>30.0
	141	0.670
	142	1.75
	144	>20.0
	145	8.5
10	146	3.8
	147	8.5
	148	30.0
	149	>30.0
	150	30.0
15	151	30.0
	152	8.8
	153	0.24
	154	0.042
	155	0.023
20	156	2.7
	157	0.26
	158	1.1
	159	8.0
	160	2.25
25	161	0.011
	162	0.0025
	163	0.0028

Example 7

30 Compounds 126, 127, 128, 129, 135a, 135b, 137
144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154,
155, 156, 157, 159, 160, 162, and 163 were synthesized

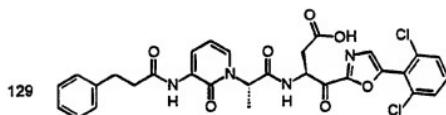
- 222 -

by a method similar to the method used in the synthesis
of 69a.

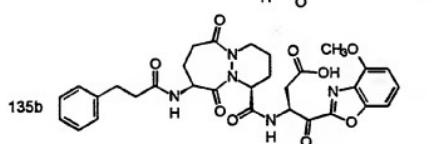
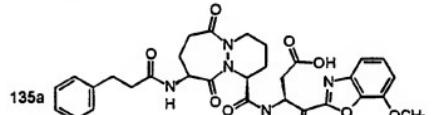


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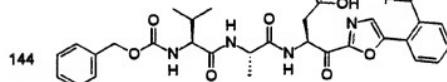
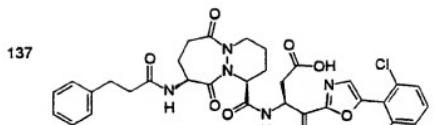
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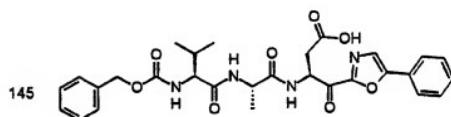
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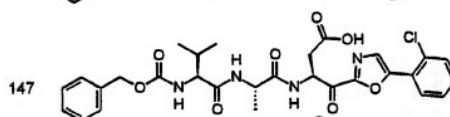
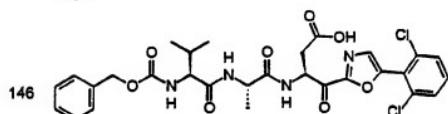
- 223 -



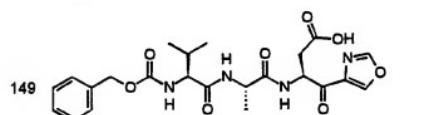
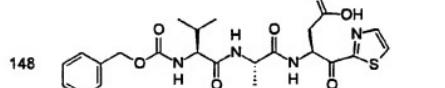
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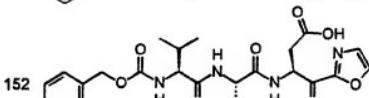
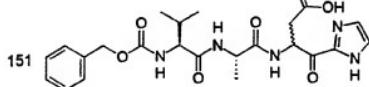
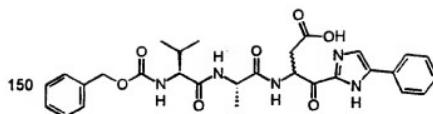


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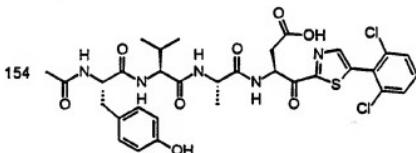
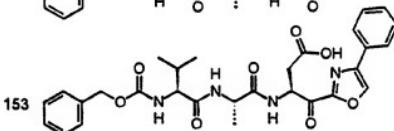


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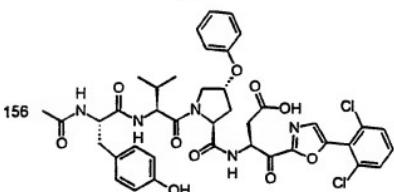
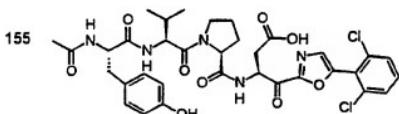
- 224 -



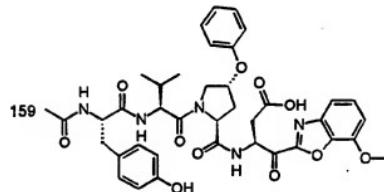
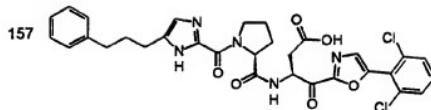
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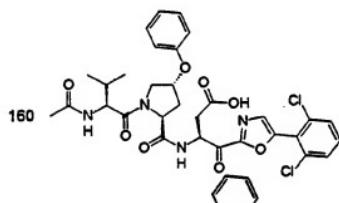
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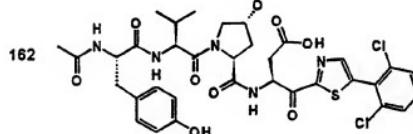
- 225 -



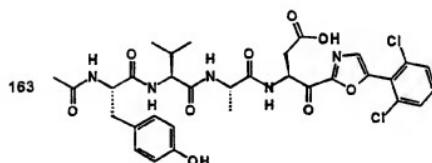
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10

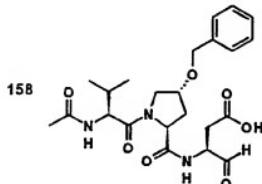


; and

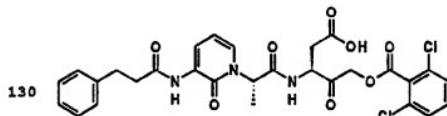


- 226 -

Compound 158 was synthesized by a method similar to the method used in the synthesis of (K).

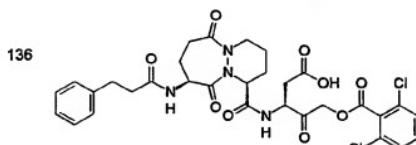
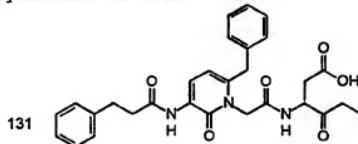


Compound 130 was synthesized by a method similar to the method used in the synthesis of 56b.



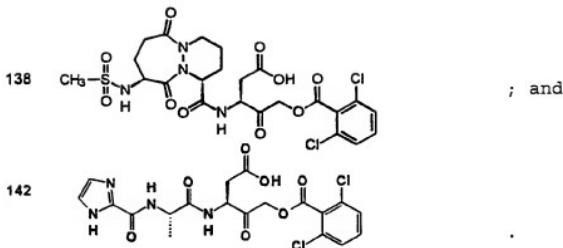
5

Compounds 131, 136, 138, and 142 were synthesized by a method similar to the method used in the synthesis of 57b.



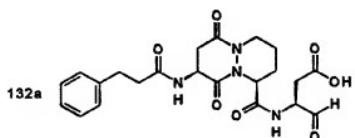
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- 227 -

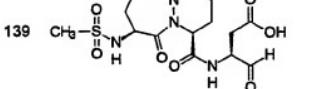
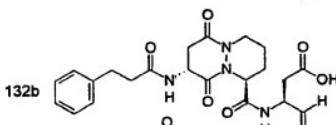


5 Compounds 132a, 132b, 139, 140, and 141 were synthesized by a method similar to the method used in the synthesis of 47a. The starting material for compound 140 was obtained as described in: Robl, et al., J. Am. Chem. Soc., 116, pp. 2348-2355 (1994). The starting material for compound 141 was obtained as described in: Wyvatt, et al., Pept. Struct. Funct. Proc. (8th Am. Pept. Symp.), (1983) or USP 4415496.

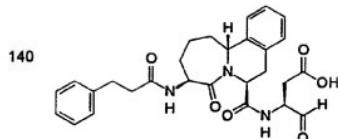
10 132a ;



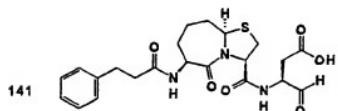
15 132b ;



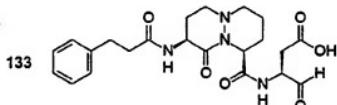
- 228 -



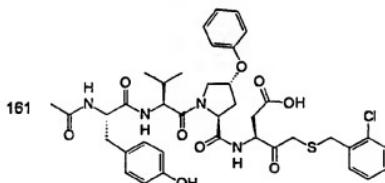
; and



Compound 133 was synthesized by a method
5 similar to the method used in the synthesis of 47b.



Compound 161 was synthesized by a method
similar to the method used in the synthesis of 125a.

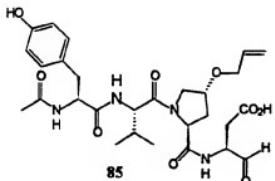


10

Compounds 22e, 54b, 54j, 54k, and 57b were
synthesized as described in example 5.

- 229 -

Compounds 85, 86, 87, 88, 89, 90, 91, 92, 98, 102a, 102b, 102c, 106a, 106b, 106c, 108a, 108b, 108c, 114a, 114b, 115, 121, 125a, and 125b were synthesized as follows.



- 5 N-(N-Acetyl-tyrosinyl-valinyl-(4(R)-allyloxy
prolinyl))-3(S)-amino-4-oxobutanoic acid (85).
Step A. N-tert-Butoxycarbonyl-4(R)-
allyloxyproline. N-tert-Butoxycarbonyl(4R)-
hydroxyproline (9.25 g, 40 mmol) was added to a
10 solution of 60% sodium hydride (3.36 g, 84 mmol) in
100 ml of anhydrous tetrahydrofuran and stirred for 2
hours at room temperature. Allyl bromide (6.9 ml, 80
mmol) was added to the mixture and refluxed for 6
hours. The mixture was quenched with the addition of
15 ice chips, then additional water was added and the
mixture was washed with hexane. The aqueous layer
was acidified with 10% sodium hydrogen sulfate and
extracted with ethyl acetate (2 x 150 ml). The
combined extracts were dried over anhydrous sodium
sulfate, filtered and evaporated to give 5 g of the
20 title product with no further purification.
¹H NMR (CDCl₃; exist as rotamers) δ 5.92-5.82 (1H,
m), 5.3-5.14 (2H, m) 4.5-4.31 (1H, m), 4.16-4.05 (1H,
m), 4.04-3.9 (1H, m), 3.79-3.5 (3H, m), 2.43-2.2
25 (1.5H, m), 2.15-2.10 (0.5H, m), 1.45 (4.5H, s), 1.35
(4.5H, s).

- 230 -

Step B. 4(R)-Allyloxyproline methyl ester hydrochloride. N-tert-Butoxycarbonyl-4(R)-allyloxyproline (5 g, 18.4 mmol) was refluxed in 50 ml of saturated methanolic hydrogen chloride for 6 hours. The mixture was evaporated in vacuo to give 3.78 g of a yellow gum as the title compound: ^1H NMR (CDCl_3) δ 5.83-5.72 (1H, m), 5.24-5.14 (1H, d), 5.13-5.08 (1H, d), 4.55-4.3 (3H, m), 4.25-4.15 (1H, m), 3.9 (1.5H, s), 3.78 (1.5H, s), 3.7-3.28 (3H, m), 2.45-2.32 (1H, m), 2.2-2.05 (1H, m).

Step C. N-Acetyl-tyrosinyl-valinyl-(4(R)-allyloxyproline) methyl ester. 4(R)-Allyloxyproline methyl ester hydrochloride (1.05 g, 4.75 mmol) and N-acetyl-Tyr-Val-OH (1.68 g, 5.21 mmol) were dissolved in 10 ml of a 1:1 mixture of dichloromethane and dimethylformamide and cooled to 0 °C. Diisopropylethylamine (1 ml, 5.93 mmol) was added to the cooled mixture followed by the addition of N-hydroxybenzotriazole (0.769 g, 5.69 mmol) and 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.18 g, 6.2 mmol). After stirring for 2 hours, the mixture was warmed to room temperature and stirred for 16 hours. The reaction was poured into 150 ml of ethyl acetate and washed with 50ml each of water, 10% sodium hydrogen sulfate, and 10% sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered, and evaporated to give a light yellow solid. This was purified by flash chromatography eluting with dichloromethane/methanol/pyridine (100:3:0.5) to give 780 mg of the title compound. ^1H NMR (CD_3OD) δ 7.02-6.96 (2H, d), 6.67-6.63 (2H, d), 5.95-5.85 (1H, m),

- 231 -

5.34-5.27 (1H, d), 5.16-5.13 (1H, d), 4.53-4.38 (3H,
m), 4.28-4.22 (1H, m), 4.12-3.97 (3H, m), 3.82-3.73
(1H, m), 3.72 (3H, s), 3.04-2.88 (2H, m), 2.85-2.72
(2H, m), 2.45-2.34 (1H, m), 2.08-1.95 (2H, m), 1.92
(3H, s), 1.00-0.92 (6H, 2 x d).

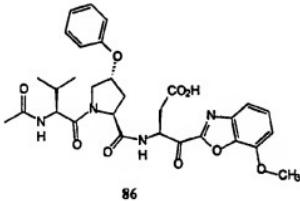
Step D. N-(N-Acetyl-tyrosinyl-valinyl-(4(R)-
allyloxyprolinyl))-3(S)-amino-4-oxobutanoic acid
tert-butyl ester semicarbazone. N-Acetyl-tyrosinyl-
valinyl-(4-allyloxyproline) methyl ester (770 mg,
10 1.57 mmol) was dissolved in 20 ml of tetrahydrofuran
and 4 ml of methanol. Lithium hydroxide (145 mg,
3.46 mmol) was added to the mixture and stirred at
room temperature. After two hours, 1 ml of 10%
hydrogen chloride was added and the mixture
15 evaporated in vacuo to give a solid residue then
partitioned between 5ml of water and 50 ml of ethyl
acetate and the organic layer separated and
evaporated in vacuo to give 430 mg of the acid that
was used immediately in the next step.

20 N-Acetyl-tyrosinyl-valinyl-4-allyloxyproline (420
mg, 0.88 mmol) and 3-amino-4-oxobutyric acid tert-
butyl ester semicarbazone (184 mg, 0.8 mol, Graybill
et al., Int. J. Protein Res., 44, pp. 173-82 (1994))
to give 100 mg (20%) of the title compound as a white
25 amorphous solid: ¹H NMR (CD₃OD) δ 7.24-7.2 (1H, m),
7.04-6.97 (2H, d), 6.73-6.65 (2H, d), 5.98-5.86 (1H,
m), 5.35-5.24 (1H, d), 5.17-5.12 (1H, m), 4.12-3.98
(2H, m), 3.72-3.67 (1H, m), 2.98-2.92 (3H, m), 2.38-
2.32 (1H, m), 2.1-2.02 (2H, m), 1.92 (3H, s), 0.98-
30 0.89 (6H, 2 x d).

- 232 -

Step E. N-(N-Acetyl-tyrosinyl-valinyl-(4(R)-allyloxyprolinyl))-3(S)-amino-4-oxobutanoic acid (85). N-(N-Acetyl-tyrosinyl-valinyl-(4(R)-allyloxyprolinyl))-3(S)-amino-4-oxobutanoic acid
 5 tert-butyl ester semicarbazone (100 mg) was deprotected as described (Example 3, compound K, Step C) to give 44.2 mg (53%) of the title compound: ^1H NMR (CD_3OD) δ 7.04-6.97 (2H, d), 6.72-6.65 (2H, d), 5.97-5.86 (1H, m), 5.32-5.25 (1H, d), 5.17-5.12 (1H, d), 4.62-4.40 (3H, m), 4.30-4.13 (2H, m), 4.12-3.96 (3H, m), 3.75-3.68 (1H, m), 2.99-2.92 (1H, m), 2.78-2.70 (1H, m), 2.70-2.48 (2H, m), 2.35-2.30 (1H, m), 2.17-1.95 (2H, m), 1.92 (3H, s), 0.98-0.88 (6H, 2 x d).

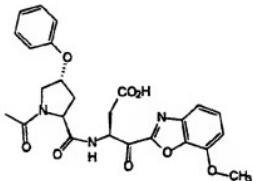
10 15 Compounds 86 and 87 were prepared by a similar method described for the synthesis of 69a in example 5:



20 N-Acetyl-(S)-valinyl-(4-(S)-phenoxy)prolinyl-3(S)-amino-4-(7-methoxybenzoxazol-2-yl)-4-oxo-butanoic acid (86). N-Acetyl-(S)-valinyl-(S)-(4-(S)-phenoxy)proline was converted to 86 as a white powder: ^1H NMR (DMSO-d_6) δ 8.75(d, 1H), 7.6-7.2(m, 4H), 7.0-6.8(m, 4H), 5.5(m, 1H), 5.05(s, 1H), 4.5(t,

- 233 -

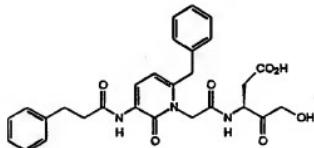
1H), 4.29(t, 1H), 4.0(s, 3H), 4.0-3.8(m, 2H), 3.0-
2.8(dd, 2H), 2.3(m, 1H), 2.09(m, 1H), 1.95-1.8(m,
2H), 1.78(s, 3H), 1-0.7(dd, 6H).



87

5 N-Acetyl(4-(R)-phenoxy)prolinyl-3(S)-amino-4-(7-methoxybenzoxazol-2-yl)-4-oxo-butanoic acid (87): N-Acetyl-(S)-(4-(S)-phenoxy)proline was converted to 87 as a white powder: ^1H NMR (DMSO-d₆) δ 9.1(d, 1H), 8.76(d, 1H), 7.6-7.2(m, 4H), 7.0-6.9(m, 4H), 5.55(m, 1H), 5.45(m, 1H), 5.0(m, 2H), 4.56(t, 1H), 4.40(t, 1H), 4.0(s, 3H), 3.9(dd, 1H), 3.76(d, 1H), 3.64(d, 1H), 3.1-2.9(m, 1H), 2.8(m, 1H), 2.50(m, 1H), 2.3-2.2(m, 1H), 2.09(m, 1H), 1.95 and 1.75(2 x s, 3H, rotamers)

10



88

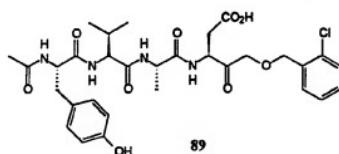
15 N-2-(6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl)acetyl-3(S)-amino-5-hydroxy-4-oxo-pentanoic acid (88). N-2-(6-Benzyl-

- 234 -

- 1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl acetyl-3(S)-amino-5-hydroxy-4-oxo-pentanoic acid tert-butyl ester was prepared from 52b and 81 following the method described for the synthesis of
 5 83a to give a white solid (45%): ^1H NMR (CDCl_3) δ 8.40(d, 1H), 8.20(s, 1H), 7.4-7.1(m, 11H), 6.18(s, 1H), 4.72(m, 1H), 4.65-4.5(q, 2H), 4.4-4.2(dd, 2H), 4.0(s, 2H), 3.04(t, 2H), 2.9(dd, 1H), 2.76(t, 2H), 2.55(dd, 1H), 1.39(s, 9H).
 10 The resulting product was converted to 88 by method described in example 5, compound 84a to give the title compound (42%) as a white solid: ^1H NMR (CDCl_3) δ 8.5(d, 1H), 8.1(d, 1H), 8.0(m, 1H), 7.4-7.1(m, 11H), 6.3(d, 1H), 4.9-4.8(m, 2H), 4.6-4.4(m, 2H),
 15 4.3(dd, 1H), 4.1(s, 2H), 3.3(t, 1H), 3.05(t, 2H), 2.8-2.6(m, 3H)

Compounds 89 and 90 were prepared by a similar method described for the preparation of 84a in example 5.

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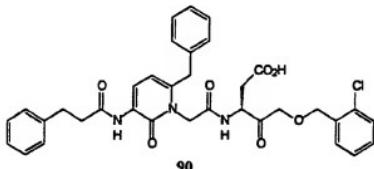


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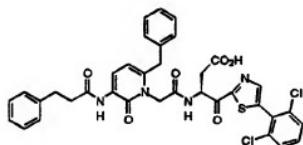
N-Acetyl-(S)-tyrosinyl-(S)-valinyl-(S)-alaninyl-3(S)-amino-5-(2-chlorobenzoyloxy)-4-oxo-pentanoic acid (89) was prepared from Ac-Tyr-Val-Ala-OH and (3S) t-butyl N-(allyloxycarbonyl)-3-amino-5-(2-chlorophenyl-methoxyl)-4-oxo-pentanoate (prepared by a similar method as 82) to give a white solid: ^1H NMR ($\text{DMSO}-\text{d}_6$)

- 235 -

d₆) δ 9.15(s, 1H), 8.5(d, 1H), 7.98(d, 1H), 7.75(d, 1H), 7.55-7.3(m, 4H), 7.0(d, 1H), 6.6(d, 2H), 4.6-4.3(m, 6H), 4.3-4.1(m, 2H), 2.9(d, 1H), 2.76(dd, 1H), 2.7-2.5(m, 2H), 1.95(m, 1H), 1.75(s, 3H), 1.2(d, 3H), 5 0.9-0.7(dd, 6H)



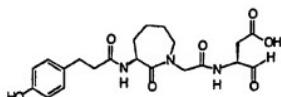
N-2-(6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl) acetyl-3-amino-5-(2-chlorobenzoyloxy)-4-oxo-pentanoic acid (90) was prepared from 52b and (3S) t-butyl N-(allyloxycarbonyl)-3-amino-5-(2-chlorophenyl-methoxyl)-4-oxo-pentanate (prepared by a similar method as 82) to give a white solid: ¹H NMR(DMSO-d₆) δ 9.2(s, 1H), 8.75(d, 1H), 7.7-7.1(m, 14H), 6.4(d, 1H), 4.65(d, 6H), 4.56(s, 1H), 4.6-4.35(dd, 1H), 15 3.9(s, 2H), 2.9-2.6(m, 6H)



N-2-(6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl) acetyl-3(S)-amino-5-(5-(2,6-dichlorophenyl) thiazol-2-yl)-4-oxo-pentanoic 20

- 236 -

acid (91) was prepared from 52b and 3-(Allyloxycarbonyl)-amino-4-[(2,6-dichloro-phenyl)-thiazol-2-yl]-4-hydroxy-butyric acid tert-butyl ester (99) as described for the preparation of 69a to give an off-white powder: ^1H NMR(DMSO- d_6) δ 9.32(s, 1H), 9.05(d, 1H), 8.27(d, 1H), 8.18(d, 1H), 7.7(d, 1H), 7.6(t, 1H), 7.4-7.1(m 1H), 6.1(d, 1H), 5.64(m, 1H), 4.8-4.6(dd, 2H), 3.85(s, 2H), 3.02(m, 1H), 2.9-2.7(m, 4H).

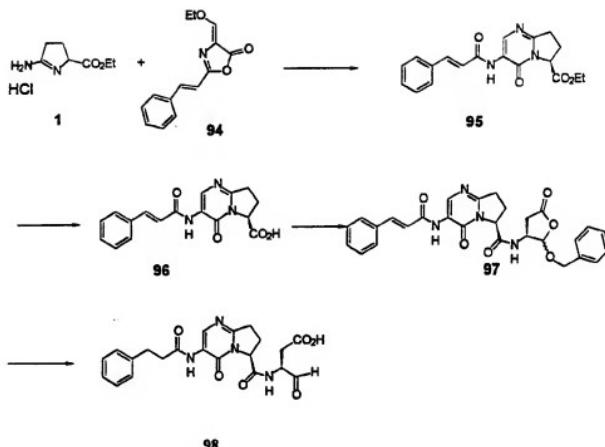


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92

3-(S)-(2-[3-[3-(S)-(4-Hydroxy-phenyl)-propionylamino]-2-oxo-azepan-1-yl)-acetylamine)-4-oxo-butyric acid (92) was prepared from 2-[3[3-(S)-(4-Hydroxy-phenyl)-propionylamino]-2-oxo-azepan-1-yl]-acetic acid and 15 N-allyloxycarbonyl-4-amino-5-benzyloxy-2-oxotetrahydrofuran (Chapman, *Bioorg. Med. Chem. Lett.*, 2, pp. 613-18 (1992)) by a similar method described for the synthesis of 54a to give the title compound as a white solid: ^1H NMR(DMSO- d_6) δ 9.10-9.20(s, 1H), 8.40(s, 1H), 7.88(d, 1H), 7.0(d, 2H), 6.64(d, 2H), 4.60(t, 1H), 4.10(q, 2H), 3.9-4.2(m, 2H), 3.6(m, 1H), 3.18(d, 2H), 2.70(t, 2H), 2.40(m, 2H), 1.85-1.40(m, 8H).

- 237 -



4-Ethoxymethylene-2-styryl-4*H*-oxazol-5-one (94) was prepared according to Cornforth, The Chemistry of Penicillin, Clarke, Johnson, Robinson, (eds.)

Princeton University Press, p. 804 (1949)

4-Oxo-3-(3-phenyl-acryloylamino)-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-(6*S*)-carboxylic acid ethyl ester (95) was prepared from 94 by the procedure in example 5 for compound 3 to give 4.5g (30%) of the title compound: ^1H NMR (CD_3OD) δ 1.3 (t, 3H), 2.35 (m, 1H), 2.65 (m, 1H), 3.1 (m, 1H), 3.15 (m, 1H), 4.25 (q, 2H), 5.15 (dd, 1H), 6.95 (d, 1H), 7.4 (m, 3H), 7.6 (m, 2H), 7.65 (d, 1H), 8.95 (s, 1H).

- 238 -

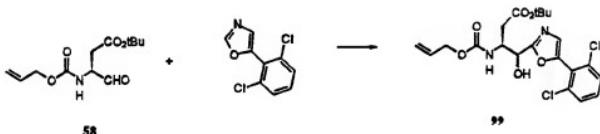
4-Oxo-3-(3-phenyl-acryloylamino)-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-(6S)-carboxylic acid (96) A mixture of 4-Oxo-3-(3-phenyl-acryloylamino)-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-(6S)-carboxylic acid ethyl ester (95, 3.1g, 8.8mmol) and aqueous 1N lithium hydroxide (8.8mL, 8.8mmol) in methanol (10mL) was stirred 18h at room temperature. The reaction was diluted with water and washed with ethyl ether (1 x 20mL). The aqueous layer was acidified with conc. hydrochloric acid. The solid was collected by filtration and washed with water. The solid was dried in a vacuum oven at 50 °C for 18h to give 2.2g (75%) of the title compound as a tan solid: ¹H NMR (CD₃OD) δ 2.4(m 1H), 2.7(m, 1H), 3.1(m, 1H), 3.2(m, 1H), 5.15(dd, 1H), 7.0(d, 1H), 7.4(m, 3H), 7.6(m, 2H), 7.65(d, 1H), 8.95(s, 1H)

4-Oxo-3-(3-phenyl-acryloylamino)-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-(6S)-carboxylic acid (2-benzyloxy-5-oxo-tetrahydro-furan-(3S)-yl)-amide (97) was prepared from 96 by the method described in example 3 for compound H, step A to give 0.52g (75%) of the title compound as a mixture of diastereomers: ¹H NMR (CDCl₃) δ 2.3-2.7(m, 3H), 2.9(dd, 1H), 3.05(m, 1H), 3.3(m, 1H), 4.4-4.8(m, 2H), 4.9(2 x d, 1H), 5.05(m, 1H), 5.55(2 x s, 1H), 6.6(2 x d, 1H), 7.4(m, 6H), 7.55(m, 4H), 7.65(2 x d, 1H), 8.0(m, 2H), 9.2(s x 2, 1H).

4-Oxo-(3S)-{[4-oxo-3-(3-phenyl-propionylamino)-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-(6S)-carbonyl]-amino}-butyric acid (98) was prepared by the procedure in example 3 for compound H, step D to

- 239 -

give 0.13g (45%) of the title compound: ${}^1\text{H}$
 NMR (CD_3OD) δ 2.35(m, 1H), 2.45-2.75(m, 3H), 2.8(t,
 2H), 3.0(t, 2H), 3.1(m, 1H), 3.25(m, 1H), 4.3(m, 1H),
 6.65(dd, 1H), 5.15(m, 1H), 7.15(m, 1H), 7.3(m, 4H),
 8.8(a, 1H).



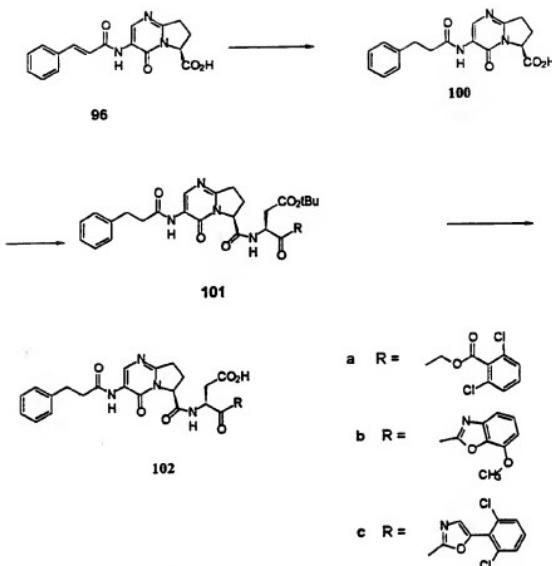
3 (S)- (Allyloxycarbonyl)-amino-4-[(2,6-dichlorophenyl)-oxazol-2-yl]-4(R,S)-hydroxy-butyric acid tert-butyl ester (99). A solution of 5-(2,6-Dichlorophenyl)oxazole (2.71g, 12.7mmol; prepared by a similar method described in *Tet. Lett.* 23, p2369 (1972)) in tetrahydrofuran (65mL) was cooled to -78 °C under a nitrogen atmosphere. To this solution was added n-butyl lithium (1.5M solution in hexanes, 8.5mL, 13.3mmol) and stirred at -78 °C for 30min. Magnesium bromide etherate (3.6g, 13.9mmol) was added and the solution was allowed to warm to -45 °C for 15min. The reaction was cooled to -78 °C and aldehyde 58 (3.26g, 12.7mmol; Graybill et al., *Int. J. Protein Res.*, 44, pp. 173-182 (1993)) in tetrahydrofuran (65mL) was added dropwise. The reaction was stirred for 25min., then allowed to warm to -40 °C and stirred for 3h, and then at room temperature for 1h. The reaction was quenched with 5% NaHCO₃ (12mL) and stirred for 3h. The tetrahydrofuran was removed in vacuo and the resulting residue was extracted with dichloromethane. The organic layer was washed with saturated sodium chloride solution and dried over magnesium sulfate,

- 240 -

filtered, and concentrated to yield 6.14g of the title compound. Purification gave 4.79g (80%) of .
99: ^1H NMR (CDCl_3) δ 1.45(s, 9H), 2.7-2.5(m, 2H),
2.8(dd, 1H), 4.2, 4.4(2 x d, 1H), 4.7-4.5(m, 3H),
5 5.35-5.1(m, 2H), 5.6, 5.7(2 x d, 1H), 6.0-5.8(m, 1H),
7.2(d, 1H), 7.3(m, 1H), 7.4(m, 2H).

10 4-Oxo-3-(3-phenyl-propionylamino)-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-(6S)-carboxylic acid (100). A mixture of 4-Oxo-3-(3-phenyl-acryloylamino)-
15 4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-(6S)-carboxylic acid (96; 2.1g, 6.5mmol) and 20% palladium hydroxide on carbon (0.5g) in methanol (50mL) was stirred under a hydrogen atmosphere for 4h. The resulting mixture was filtered and concentrated to yield 2.1g (100%) of the title compound as a white solid: ^1H NMR(CD_3OD) δ 2.35(m, 1H), 2.65(m, 1H),
2.75(t, 2H), 3.0(t, 2H), 3.1(m, 1H), 3.15(m, 1H),
5.1(dd, 1H), 7.15(m, 1H), 7.25(m, 4H), 8.75(s, 1H)

- 241 -



2,6-Dichloro-benzoic acid 4-tert-butoxycarbonyl-2-oxo-(3*S*)-{[4-oxo-3-(3-phenyl-propionylamino)-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-(6*S*)-carbonyl]-amino}-butyl ester (101a) was prepared by the procedure in example 5 for compound 56a to give 0.16g (20%) of the title compound: ^1H NMR(CD₃OD) δ 1.45(s, 9H), 2.3(m, 1H), 2.6(m, 1H), 2.7(m, 3H), 2.95(m, 3H), 4.8(m, 1H), 5.1(m, 1H), 5.2(q, 2H), 7.1(m, 1H), 7.2(m, 4H), 7.4(m, 3H), 8.75(s, 1H).

10 4-(7-methoxy-benzoxazol-2-yl)-4-oxo-(3*S*)-{[4-oxo-3-(3-phenyl-propionylamino)-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-(6*S*)-carbonyl]-amino}-butric

- 242 -

acid tert-butyl ester (101b). 4-Hydroxy-4-(7-methoxy-benzoxazol-2-yl)-(3S)-{[4-oxo-3-(3-phenyl-propionylamino)-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-(6S)-carbonyl]-amino}-butyric acid tert-butyl ester was prepared from 100 and 66a by the procedure in example 5 for compound 67a to give 0.95g (quantitative) of the product as a mixture of diastereomers: ^1H NMR(CD₃OD) δ 1.45(2 x s, 9H), 2.2(2 x m, 1H), 2.35-3.0(m, 9H), 4.0(m, 3H), 4.75(m, 1H), 4.85(m, 1H), 5.05(2 x dd, 1H), 7.1(2 x dd, 1H), 7.15-7.3(m, 4H), 7.5(2 x t, 1H), 7.8(2 x d, 1H), 8.55(2 x dd, 1H), 8.7(2 x s, 1H).

The resulting product was converted to 101b by the procedure in example 5 for compound 68a to give 0.36g (50%) of the title compound: ^1H NMR(CD₃OD) δ 1.4(s, 9H), 2.35(m, 1H), 2.55(m, 1H), 2.75(t, 2H), 2.95(t, 2H), 3.00(m, 1H), 3.1(dd, 2H), 3.15(m, 1H), 5.15(dd, 1H), 5.65(t, 1H), 7.1(m, 2H), 7.2(m, 4H), 7.4(m, 2H), 8.7(s, 1H)

4-[5-(2,6-Dichloro-phenyl)-oxazol-2-yl]-4-oxo-(3S)-{[4-oxo-3-(3-phenyl-propionylamino)-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-(6S)-carbonyl]-amino}-butyric acid tert-butyl ester (101c). 4-[5-(2,6-Dichloro-phenyl)-oxazol-2-yl]-4-hydroxy-(3S)-{[4-oxo-3-(3-phenyl-propionylamino)-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-(6S)-carbonyl]-amino}-butyric acid tert-butyl ester from 100 and 99 using the method described in example 5, compound 67a to give 0.09g (60%) of the product as a mixture of diastereomers: ^1H NMR(CD₃OD) δ 1.45(2 x s, 9H), 2.2(m, 1H), 2.5(m, 2H), 2.7(2 x dd, 1H), 2.75(t, 2H),

- 243 -

2.9-3.1(m, 4H), 4.7(m, 1H), 5.1(m, 2H), 7.1(m, 1H),
7.1-7.25(m, 4H), 7.4(t, 1H), 7.5(t, 1H), 8.55(d, 1H),
8.75(s, 1H).

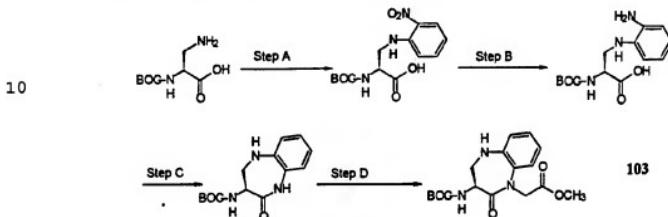
5 The resulting product was converted to 101c by the
method described in example 5, compound 68a to give
0.04g (45%) of the title compound: ^1H NMR(CD₃OD) δ
1.4(s, 9H), 2.3(m, 1H), 2.6(m, 1H), 2.75(t, 2H),
2.95(t, 2H), 2.9-3.2(m, 4H), 5.2(dd, 1H), 5.55(t,
1H), 7.1(m, 1H), 7.25(m, 4H), 7.55(m, 3H), 8.75(s,
1H).

10 2,6-Dichloro-benzoic acid 4-carboxy-2-oxo-(3S)-{[4-
oxo-3-(3-phenyl-propionylamino)-4,6,7,8-tetrahydro-
pyrrolo[1,2-a]pyrimidine-(6S)-carbonyl]-amino}-butyl
ester (102a) was prepared from 101a by the procedure
15 in example 5 for compound 57a to give 0.12g (80%) of
the title compound: ^1H NMR(CD₃OD) δ 2.35(m, 1H),
2.65(m, 1H), 2.75(m, 2H), 2.85(dd, 1H), 2.95(m, 2H),
3.0(dd, 1H), 3.15(m, 1H), 3.25(m, 1H), 4.55(dd, 1H),
5.15(m, 1H), 5.25(q, 2H), 7.15(m, 1H), 7.25(m, 4H),
20 7.45(m, 1H), 8.8(s, 1H).

25 4-(7-methoxy-benzoxazol-2-yl)-4-oxo-(3S)-{[4-oxo-3-(3-
phenyl-propionylamino)-4,6,7,8-tetrahydro-pyrrolo [1,2-
a]pyrimidine-(6S)-carbonyl]-amino}-butric acid (102b) was
prepared from 101b by the procedure described in example 5
for compound 69a to give 0.12g (35%) of the title
compound: ^1H NMR(DMSO-d₆) δ 2.1(m, 1H), 2.55(m, 1H), 2.7-
3.1(m, 8H), 4.05(s, 3H), 5.1(dd, 1H), 5.55(t, 1H), 7.2(m,
1H), 7.25(m, 5H), 7.5(t, 1H), 7.55(d, 1H), 8.7(s, 1H),
9.2(d, 1H), 9.4(s, 1H), 12.7(br, 1H).

- 244 -

4-[5-(2,6-Dichloro-phenyl)-oxazol-2-yl]-4-oxo-(3S)-{[4-oxo-3-(3-phenyl-propionylamino)-4,6,7,8-tetrahydro-pyrrolo[1,2-a] pyrimidine-(6S)-carbonyl]-amino}-butyric acid (102c) was prepared from 101c as described in example 5 for compound 69a to give 0.01g (40%) of the title compound: ^1H NMR (CD₃OD) δ 2.35(m, 1H), 2.6(m, 1H), 2.75(t, 2H), 2.95(t, 2H), 3.05(m, 1H), 3.15(m, 3H), 5.15(dd, 1H), 5.55(t, 1H), 7.15(m, 1H), 7.2(m, 4H), 7.55(m, 3H), 8.8(s, 1H)



(3-tert-Butoxycarbonylamino-2-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl)acetic acid methyl ester (103).

Step A. 2(S)-tert-Butoxycarbonylamino-3-(2-nitrophenyl-amino)-propionic acid. 2-tert-Butoxycarbonylamino-3-aminopropionic acid (10 g, 49 mmol), 2-fluoronitrobenzene (5.7 ml, 54 mmol), and sodium bicarbonate (8.25 g, 98 mmol) was taken into 130 ml of dimethylformamide and heated at 80 °C for 18 hours. The reaction was evaporated in vacuo to give a viscous orange residue that was dissolved in 300 ml of water and extracted with diethyl ether (3 x 150 ml). The aqueous solution was acidified to pH 5 with 10 % sodium hydrogen sulfate and extracted with

- 245 -

ethyl acetate (3 x 250 ml). The combined extracts were dried over anhydrous sodium sulfate, filtered, and evaporated to give 12.64 g (83 %) of the title compound as an orange amorphous solid. ¹H NMR (CD₃OD) δ 8.15-8.10 (1H, d), 7.54-7.48 (1H, t), 7.13-7.08 (1H, d), 6.73-6.65 (1H, t), 4.45-4.35 (1H, m), 3.9-3.8 (1H, dd), 3.65-3.55 (1H, dd), 1.45 (9H, s).

Step B. 2(S)-tert-Butoxycarbonylamino-3-(2-aminophenyl-amino)-propionic acid. A mixture of 2-tert-Butoxycarbonylamino-3-(2-nitrophenylamino)propionic acid (12.65 g, 40.5 mmol) and 0.5 g of 10% Pd/C in 100 ml of methanol under hydrogen at 1 atmosphere was stirred for 4 hrs. The solution was filtered through Celite 545 and the filtrate evaporated in vacuo to afford 11.95 g of the title compound in quantitative yield as a dark brown solid that was used without purification. ¹H NMR (CD₃OD) δ 6.75-6.70 (3H, m), 6.65-6.58 (1H, m), 4.35-4.3 (1H, m), 3.6-3.38 (2H, m), 1.45 (9H, s).

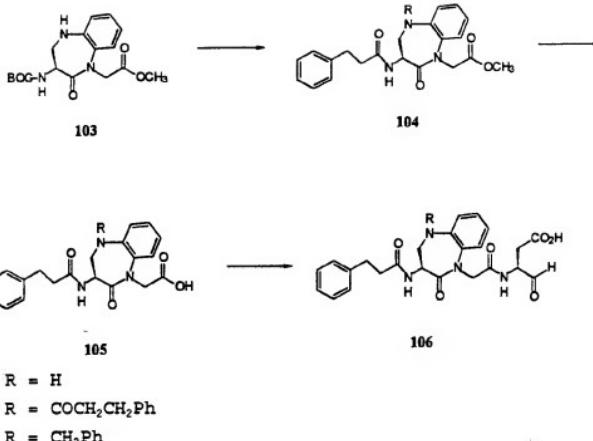
Step C. 3(S)-tert-Butoxycarbonylamino-1,3,4,5-tetrahydro-benzo[b] [1,4] diazepin-2-one. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (8.54 g, 44.5 mmol) was added to a cooled (0 °C) solution of 2-tert-butoxycarbonylamino-3-(2-aminophenylamino)propionic acid (11.95 g, 40.5 mmol) in 100 ml of dimethylformamide and stirred for 18 hours. The reaction was poured into 700 ml of ethyl acetate and washed four times with 100 ml of water. The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to give a brown solid that was purified by flash chromatography.

- 246 -

eluting with 3:7 ethyl acetate/hexane to give 8 g
(71%) of the title compound: ^1H NMR (CDCl_3) δ 7.78 (1H,
s), 7.02-6.95 (1H, m), 6.88-6.82 (1H, m), 6.82-6.78
(1H, m), 6.75-6.70 (1H, m), 5.8-5.7 (1H, d), 4.55-4.45
5 (1H, m), 3.95 (1H, s), 3.9-3.82 (1H, m), 3.48-3.40
(1H, m), 1.45 (9H, s).

Step D. (3(S)-tert-Butoxycarbonylamino-2-oxo-
2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl)acetic
acid methyl ester (103). A 1.0 M solution of lithium
10 bis(trimethylsilyl)amide (3.4 ml, 3.4 mmol) in THF was
added dropwise to a -78 °C solution of 3-tert-
butoxycarbonylamino-1,3,4,5-
tetrahydrobenzo[b][1,4]diazepin-2-one (0.94 g, 3.38
mmol) in 20 ml of anhydrous tetrahydrofuran and
15 stirred for 30 minutes. Methyl bromoacetate (0.44 ml,
4 mmol) was added dropwise to the reaction mixture
then warmed to room temperature. The reaction was
diluted with 100 ml of ethyl acetate and washed with
0.3N potassium hydrogen sulfate (50 ml), water (2 x 50
ml), and brine. The combined organics were dried over
20 anhydrous sodium sulfate, filtered, and evaporated to
afford a gum that was purified by flash chromatography
eluting with 3:7 EtOAc/Hex. to give 0.98 g (83%) of
the title compound as a white solid. ^1H NMR (CDCl_3) δ
25 7.15-7.07 (2H, m), 6.98-6.94 (1H, m), 6.88-6.84 (1H,
d), 5.62-5.55 (1H, d), 4.71-4.65 (1H, d), 4.65-4.6
(1H, m), 4.33-4.27 (1H, d), 3.96-3.90 (1H, m), 3.78
(3H, s), 3.44-3.37 (1H, m), 1.4 (9H, s).

- 247 -



5 [2-Oxo-3(S)-[3-phenylpropionylamino]-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid methyl ester (104a). Anhydrous hydrogen chloride was bubbled into a solution of (3(S)-tert-butoxycarbonylamino-2-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl)acetic acid methyl ester (103, 1g, 10 2.86 mmol) in 25 ml of ethyl acetate for 2 minutes then stirred for 1 hour at room temperature. The reaction was evaporated to give 2-oxo-3(S)-amino-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl acetic acid methyl ester hydrochloride as a white solid.

10 The hydrochloride salt and hydrocinnamic acid (0.47 g, 15 3.15 mmol) was dissolved into 20 ml of dimethylformamide and cooled to 0 °C. Diisopropylethylamine (1 ml, 5.72 mmol) was added to the solution followed by the addition of N-hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. After stirring for

- 248 -

18 hours at room temperature, the mixture was diluted with 150 ml of ethyl acetate and washed with 10% sodium hydrogen sulfate, 10% sodium bicarbonate, and brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to a crude solid that was purified by flash chromatography eluting with 7:3 ethyl acetate/dichloromethane to afford 600 mg (55%) of the title compound as a white solid. ¹H NMR (CDCl₃) δ 7.3-6.85 (9H, m), 6.55-6.0 (1H, d), 4.88-4.82 (1H, m), 4.72-4.65 (1H, d), 4.28-4.22 (1H, m), 3.95-3.9 (1H, m), 3.78 (3H, s), 3.65 (1H, br. s), 3.28-3.2 (1H, m), 2.95-2.84 (2H, m), 2.55-2.4 (2H, m).

(3(S)-{(3-Phenylpropionylamino)-2-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl)acetic acid (105a). (3(S)-{(3-Phenylpropionylamino)-2-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl)acetic acid methyl ester (104a) was dissolved in 90% methanol. Lithium hydroxide hydrate was added to the reaction and the reaction was stirred at room temperature for 4 h. The reaction was evaporated in vacuo to give a white solid. This was dissolved in 20 ml of water and acidified to pH 5 and extracted with ethyl acetate to afford 304 mg (88%) of the title compound as a white solid. ¹H NMR (CDCl₃) δ 7.5-6.9 (11H, m), 4.92-4.8 (1H, m), 4.7-4.58 (1H, d), 4.38-4.25 (1H, d), 3.88-3.78 (1H, m), 3.45-3.25 (1H, m), 3.05-2.85 (2H, m), 2.55-2.45 (2H, m).

4-Oxo-3(S)-{2-[2-oxo-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-ylacetylamino}butyric acid (106a). N-[1-(2-Benzylxy-

- 249 -

5-oxotetrahydrofuran-3-ylcarbamoyl-methyl)- 2-oxo-
2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-3-
phenylpropionamide was prepared from 105a by the
procedure in example 3, compound H (stepA) to afford
5 390 mg (93%) of the product as diastereomers. ¹H NMR
(CD₃OD) δ 7.58-7.22 (14H, m), 5.78-5.73 (0.5 H, d),
5.64 (0.5 H, s), 5.0-4.72 (4H, m), 4.54-4.42 (2H, m),
3.82-3.76 (0.5 H, m), 3.68-3.62 (0.5 H, m), 3.28-3.21
(0.5H, m), 3.19-3.12 (0.5H, m), 3.07-2.98 (2H, m),
10 2.78-2.48 (4H, m).
The resulting product was converted to 106a by the
method described in example 3, compound H (StepD) to
afford the title compound as a white solid (17%): ¹H
NMR (CD₃OD) δ 7.54-6.98 (9H, m), 5.58-5.44 (1H, m),
15 4.8-4.2 (4H, m), 3.96-3.3 (2H, m), 3.30-3.05 (1H, m),
2.98-2.25 (5H, m).

[2-Oxo-5-(3-phenylpropionyl)-3(S)-(3-
phenylpropionylamino)-2,3,4,5-
tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid
20 methyl ester (104b). Anhydrous hydrogen chloride was
bubbled into a solution of (3(S)-tert-
butoxycarbonylamino-2-oxo-2,3,4,5-tetrahydro-
benzo[b][1,4]diazepin-1-yl)acetic acid methyl ester
(103, 1g, 2.86mmol) in 25 ml of ethyl acetate for 2
25 minutes then stirred for 1 hour at room temperature.
The reaction was evaporated to give 2-oxo-3(S)-amino-
2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl acetic
acid methyl ester hydrochloride as a white solid.
The hydrochloride salt was suspended into 20 ml of
30 dichloromethane and cooled to 0 °C. Triethylamine
(1.6 ml, 11.5 mmol) was added to the suspension
followed by the dropwise addition of dihydrocinnamoyl

- 250 -

chloride (0.9 ml, 6 mmol). The mixture was warmed to room temperature and stirred for 18 hours. The mixture was diluted with 25 ml of dichloromethane and washed twice with 50 ml of water and once with 50 ml of brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to give a viscous, yellow oil that was purified by flash chromatography eluting with 1:1 ethyl acetate/dichloromethane to afford 1.35 g (92%) of the title product as a white solid. ^1H NMR (CDCl_3) δ 7.45-7.02 (14 H, m), 6.37-6.32 (1H, d), 4.78-4.72 (1H, m), 4.52-4.3 (3H, m), 3.82-3.77 (1H, m), 3.74 (3H, s), 3.03-2.87 (4H, m), 2.58-2.45 (2H, m), 2.45-2.35 (1H, m), 2.25-2.16 (1H, m).

[2-Oxo-5-(3-phenylpropionyl)-3-(3(S)-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid (105b). [2-Oxo-5-(3-phenylpropionyl)-3-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid methyl ester (104b; 680 mg, 1.32 mmol) was hydrolyzed by the procedure in example 105a to afford 645 mg (98%) of the title compound as a white solid. ^1H NMR (CDCl_3) δ 7.58 (1H, br. s), 7.5-7.42 (1H, m), 7.35-6.95 (14H, m), 4.95-4.88 (1H, m), 4.64-4.55 (1H, d), 4.54-4.45 (1H, t), 4.15-4.05 (1H, d), 3.75 (1H, m), 3.05-2.75 (4H, m), 2.58-2.45 (2H, m), 2.45-2.28 (1H, m), 2.25-2.14 (1H, m).

2-Oxo-3(S)-{2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-phenyl-propionyl-amino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]}

- 251 -

acetylamino}butyric acid (106b). [2-Oxo-5-(3-phenylpropionyl)-3-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b] [1,4]diazepin-1-yl]acetic acid and 3-amino-4-oxobutyric acid tert-butylester
5 semicarbazone were coupled by the procedure in example 3, compound K (step A) to give 350 mg (85%) of a white solid. ^1H NMR (CDCl_3) δ 9.05 (1H, br. s), 7.58-7.55 (1H, d), 7.5-7.35 (1H, m), 7.35-6.95 (14 H, m), 6.75-6.72 (1H, d), 6.25 (1H, br. s), 5.25 (1H, br. s), 4.95-4.88 (1H, m), 4.8-4.72 (1H, m), 4.55-4.4 (2H, m), 3.92-3.88 (1H, d), 3.73-3.68 (1H, m), 2.95-2.8 (4H, m), 2.8-2.72 (1H, m), 2.62-2.55 (1H, m), 2.55-2.45 (2H, m), 2.4-2.32 (1H, m), 2.2-2.12 (1H, m), 1.45 (9H, s).
10 4-Oxo-3-{2-[2-oxo-5-(3-phenylpropionyl)-3-(3-phenylpropionyl -amino)-2,3,4,5-
15 tetrahydrobenzo[b] [1,4]diazepin-1-yl]-acetyl-
amino}butyric acid tert-butyl ester semicarbazone was deprotected as described in example 3, compound K
20 (step C) to give 118 mg (47%) of the title compound as a white solid. ^1H NMR (CD_3OD) δ 7.48-6.95 (14 H, m), 4.65-4.15 (6H, m), 3.5-3.4 (1H, m), 2.85-2.72 (4H, m), 2.65-2.5 (1H, m), 2.5-2.34 (3H, m), 2.34-2.15 (2H, m).
25 [5-Benzyl-2-oxo-3(S)-(3-phenylpropionylamino)-2,3,4,5-
tetrahydro -benzo[b] [1,4]diazepin-1-yl]acetic acid
methyl ester (104c). [2-Oxo-3-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo-[b] [1,4]diazepin-1-yl]acetic acid methyl ester (104a;
30 500 mg, 1.31 mmol), calcium carbonate (155 mg, 1.58 mmol), and benzyl bromide (170 μl , 1.44 mmol) were taken into 10 ml of dimethylformamide and heated to 80 °C for 8 hours. The mixture was diluted with 150 ml

- 252 -

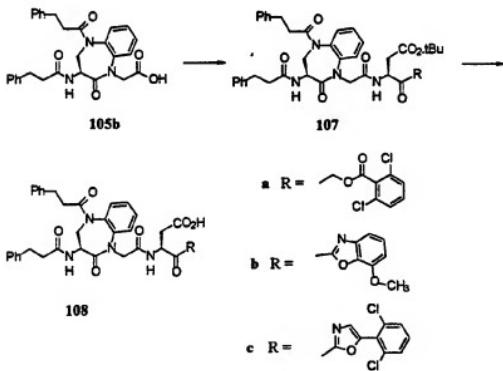
of ethyl acetate and washed 4 times with 50 ml of water. The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to give a viscous, yellow oil that was purified by flash chromatography eluting with dichloromethane/ethyl acetate (8:2) to give 460 mg (75%) of the title compound as a white solid. ^1H NMR (CDCl_3) δ 7.34-7.05 (14 H, m), 6.32-6.28 (1H, d), 4.84-4.76 (1H, d), 4.76-4.70 (1H, m), 4.43-4.37 (1H, d), 4.26-4.18 (1H, d), 4.06-4.00 (1H, d), 3.79 (3H, s), 3.45-3.37 (1H, m), 3.02-2.95 (1H, m), 2.90-2.82 (2H, m), 2.5-2.34 (2H, m).

[5-Benzyl-2-oxo-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-yl]acetic acid (105c) was prepared by the hydrolysis of the ester (102c) by the procedure reported in example 105a to give 450 mg (98%) of the title compound as a white solid: ^1H NMR (CD_3OD) δ 7.5-7.05 (14 H, m), 6.4 (1H, br. s), 4.85-4.55 (2H, m), 4.5-4.21 (2H, m), 4.12-3.92 (1H, d), 3.45-3.3 (1H, m), 3.1-2.8 (3H, m), 2.55-2.28 (3H, m).

3(S)-{2-[5-Benzyl-2-oxo-3-(3(S)-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-acetyl amino}-4-oxobutyric acid (106c). [5-Benzyl-2-oxo-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-yl]acetic acid and 3(S)-amino-4-oxobutyric acid tert-butylester semicarbazone were coupled by the procedure in example 3, compound K (step A) and to afford 260 mg (85%) of a white solid: ^1H NMR (CD_3OD) δ 7.35-7.0 (15 H, m), 4.94-4.88 (1H, m), 4.68-4.58 (1H, d), 4.57-4.52 (1H, m), 4.41-4.34

- 253 -

(1H, d), 4.3-4.23 (1H, d), 4.1-4.04 (1H, d), 3.18-3.11
 (1H, m), 3.09-2.98 (1H, m), 2.78-2.72 (2H, t), 2.65-
 2.57 (1H, m), 2.42-2.33 (3H, m).
 5 3(S)-{2-[5-Benzyl-2-oxo-3(S)-(3-phenylpropionylamino)-
 2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-
 acetylamino}-4-oxobutyric acid tert-butyl ester
 semicarbazone was deprotected as described in example
 3, compound K (step C) to give 168 mg (81%) of the
 title compound as a white solid. ^1H NMR (CD_3OD) δ
 10 7.37-7.0 (14H, m), 4.75-4.62 (1H, m), 4.6-4.45 (2H,
 m), 4.4-4.21 (2H, m), 4.15-3.95 (2H, m), 3.15-3.0 (2H,
 m), 2.82-2.67 (2H, m), 2.65-2.52 (1H, m), 2.5-2.32
 (3H, m).



15 2,6-Dichlorobenzoic acid 4-tert-butoxycarbonyl-2-oxo-
3(S)-{2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-
phenylpropionylamino)-2,3,4,5-tetrahydro-
benzo[b][1,4]diazepin-1-yl]acetyl-amino}butyl ester
(107a). The resulting semicarbazone was prepared by
the coupling of compound 105b and t-butyl 3-

- 254 -

(allyloxycarbonylamino)-4-oxo-5-(2,6-dichlorobenzoyl-oxy)pentanoate (WO 93 16710) as described in compound 56a to give 256 mg (58%) of the title compound as a white solid. ^1H NMR (CDCl_3) δ 7.45-7.04 (17H, m), 6.45-6.34 (2H, m), 5.28-5.21 (1H, m), 5.1-5.0 (1H, m), 4.95-4.90 (1H, m), 4.75-4.70 (1H, m), 4.55-4.44 (1H, m), 4.32-4.22 (1H, dd), 3.99-3.85 (1H, dd), 3.85-3.76 (1H, m), 3.06-2.83 (5H, m), 2.83-2.74 (1H, m), 2.6-2.44 (2H, m), 2.43-2.33 (1H, m), 2.24-2.15 (1H, m), 1.45 (9H, s).

2,6-Dichlorobenzoic acid 4-carboxy-2-oxo-3(S)-{2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetylamino}butyl ester (108a) was prepared from 107a by the method described for compound 57a which afforded 156 mg (68%) of the title compound as a white solid. ^1H NMR (CD_3OD) δ 7.5-6.9 (17H, m), 5.16-5.02 (1H, dd), 4.88-4.71 (2H, m), 4.62-4.44 (2H, m), 4.42-4.28 (2H, m), 4.27-4.18 (1H, m), 3.47-3.41 (1H, m), 2.90-2.60 (5H, m), 2.46-2.4 (2H, m), 2.39-2.18 (2H, m).

4-(7-Methoxybenzoxazol-2-yl)-4-oxo-3(S)-{2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-acetylamino} butyric acid tert-butyl ester (107b). 4(R,S)-Hydroxy-4-(7-methoxybenzoxazol-2-yl)-3(S)-{2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydro[b][1,4]diazepin-1-yl-acetylamino} butyric acid tert-butyl ester was prepared from 105b and 66a by the method described in example 5, compound 67 to

- 255 -

give 56% of a white solid: ^1H NMR (CDCl_3) δ 7.72-6.78 (19H, m), 6.37-6.28 (1H, m), 5.17-5.08 (0.5H, m), 4.92-4.82 (0.5H, m), 4.81-4.6 (1H, m), 4.6-4.35 ((3H, m), 4.05-3.9 (1H, m), 3.95 (3H, s), 3.82-3.7 (1H, m), 2.96-2.05 (10H, m), 1.45 (4.5H, s), 1.38 (4.5H, s).

The resulting product was converted to 107b by the method described in example 5, compound 68a to give the title compound (56%) as a white solid. ^1H NMR (CD_3OD) δ 7.62-6.8 (17H, m), 5.64-5.58 (0.5H, t), 5.52-5.46 (0.5H, t), 4.62-4.47 (2H, m), 4.40-4.32 (1H, m), 3.9 (1.5H, s), 3.88 (1.5 H, s), 3.43-3.37 (1H, m), 3.0-2.92 (1H, m), 2.90-2.62 (6H, m), 2.5-2.4 (2H, m), 2.28-2.15 (2H, m), 1.32 (4.5H, s), 1.25 (4.5H, s).

15 4-(7-Methoxybenzoxazol-2-yl)-4-oxo-3(S)-{2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b] [1,4]diazepin-1-yl]-acetylamino} butyric acid (108b) was prepared by the method described in example 5, compound 69a to give
20 the title compound (50%) as a white solid. ^1H NMR (CD_3OD) δ 7.41-6.88 (17H, m), 5.6-5.55 (0.5H, t), 5.48-5.43 (0.5H, t), 4.64-4.45 (2H, m), 4.45-4.30 (1H, m), 3.93 (1.5H, s), 3.90 (1.5H, s), 3.47-3.34 (1H, m), 3.10-2.85 (2H, m), 2.84-2.63 (5H, m), 2.6-2.4 (2H, m), 2.3-2.1 (2H, m).

25 4-[5-(2,6-Dichlorophenyl)oxazol-2-yl]-4-oxo-3(S)-{2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b] [1,4]diazepin-1-yl]-acetylamino} butyric acid tert-butyl ester (107c). 4-[5-(2,6-Dichlorophenyl)oxazol-2-yl]-4(R,S)-hydroxy-3(S)-{2-[2-

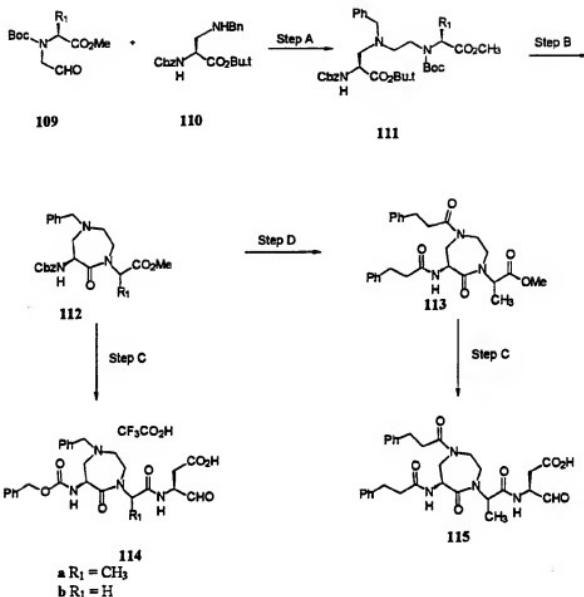
- 256 -

oxo- 5-(3-phenylpropionyl)-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-acetylamino} butyric acid tert-butyl ester was prepared from 106c and 99 by a similar method as described for compound 67a in example 5 to give 72% of a white solid. ¹H NMR (CDCl₃) δ 7.71-7.64 (1H, m), 7.58-7.42 (2H, m), 7.42-6.92 (15H, m), 6.5-6.37 (2H, m), 5.15-5.04 (1H, m), 4.88-4.68 (2H, m), 4.57-4.37 (2H, m), 4.28-4.13 (1H, m), 3.87-3.64 (2H, m), 3.04-2.80 (4H, m), 2.76-2.68 (1H, m), 2.67-2.42 (3H, m), 2.41-2.31 (1H, m), 2.22-2.12 (1H, m), 1.45 (9H, s). The resulting product was converted to 107c by a similar method as described for compound 68a in example 5 to give the title compound in quantitative yield as a white solid. ¹H NMR (CDCl₃) δ 7.47-6.98 (18H, m), 6.52-6.42 (1H, d), 5.6-5.52 (1H, m), 4.78-4.71 (1H, m), 4.52-4.40 (2H, m), 4.03-3.94 (0.67H, m), 3.94-3.85 (0.33H, m), 3.85-3.75 (1H, m), 3.45-3.33 (1H, m), 3.08-2.98 (1H, m), 2.97-2.84 (4H, m), 2.55-2.43 (2H, m), 2.43-2.32 (1H, m), 2.23-2.13 (1H, m), 1.35 (9H, s).

4-[5-(2,6-Dichlorophenyl)oxazol-2-yl]-4-oxo-3(S)-{2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-acetylamino} butyric acid (108c) was prepared from 107c by a similar method as described for compound 69a in example 5 to give 72% the title compound as a white solid. ¹H NMR (CD₃OD) δ 7.58-7.0 (18H, m), 5.62-5.53 (0.67H, m), 5.52-5.47 (0.33H, m), 4.68 (3H, m), 3.54-3.42 (1H, m), 3.1-2.92 (2H, m), 2.88-2.68 (5H, m),

- 257 -

2.63-2.45 (2H, m) 2.40-2.22 (2H, m).



3 (S) - {2 (R, S) - [4-Benzyl-7-oxo-6 (S) - (N-benzyloxycarbonylamino) - [1, 4] diazepan-1-yl] - propionylamino} - 4-oxo-butyric acid trifluoroacetic acid salt (114a):

Step A. To a solution of *tert*-butyl-2-N-benzyloxycarbonyl-3-N-benzyl-(S)-2,3-diaminopropionate (**110**; 0.85 g, 2.2 mmol), 3-(N-*tert*-butoxycarbonyl)amino-2-methyl-5-oxo-pentanoic acid methyl ester (**109a**; 0.65 g, 2.7 mmol), acetic acid (0.1 mL, 1.8 mmol), sodium acetate (0.36 g, 2

- 258 -

mmol) and 4 Å molecular sieves (1 g) in methanol (45 mL), was added sodium cyanoborohydride (0.33 g, 5.3 mmol). The mixture was stirred overnight at 25 °C then filtered through Celite and concentrated under reduced pressure. The residue was dissolved in 1 N NaOH and extracted with ethyl acetate (3 x 40 mL). The organic layer was dried (MgSO_4), filtered and evaporated to give an oil. Chromatography (silica-gel, 4:1 hexane: ethyl acetate as eluent) gave 0.92 g (68% yield) of 111a as an oil.

Step B. The above material was dissolved in dichloromethane (3 mL) cooled to 0 °C and treated with a 25% solution of trifluoroacetic acid in dichloromethane (20 mL) then allowed to warm to 25 °C and stir until the reaction was judged complete by TLC (4:1 hexane: ethyl acetate). The solvent was removed under reduced pressure and the residue dried under vacuum then dissolved in dichloromethane (40 mL) and treated with 4-methylmorpholine (1 mL, 9 mmol), HOBT (0.2g, 1.5 mmol) and EDC (0.61 g, 3.2 mmol). The resulting mixture was stirred overnight at 25 °C then diluted with dichloromethane and washed with water. The organic layer was dried (MgSO_4), filtered and evaporated to give an oil.

Chromatography (silica-gel, 3:2 hexane: ethyl acetate) gave 0.49 g (74% yield) of 112a as a viscous oil.

Step C. A solution of 2(R,S)-[4-benzyl-7-oxo-6(S)-(N-benzyloxycarbonylamino)-[1,4]diazepan-1-yl]-propionic acid methyl ester (112a; 0.15 g, 0.32 mmol) was dissolved in methanol and treated with 1 M LiOH (0.32 mL) and stirred 5.5 hours at 25 °C then evaporated to dryness. The residue was azeotroped with ethanol (2 x 10 mL), acetonitrile (2 x 10 mL),

- 259 -

benzene (2 x 10 mL) then dried under vacuum. The resulting residue was converted to 114a by a method similar to that described in example 3, compound K (steps A, B, and C) and purified by reverse phase (C18 column) HPLC using 0.1%TFA:water/ 5 0.1%TFA:acetonitrile as eluent. to give 17 mg (10% yield) of a viscous oil: ^1H NMR (500 MHz, CD₃OD) δ 1.15 (m, 3 H), 2.30- 2.70 (m, 6 H), 2.72- 2.95 (bm, 6 H), 3.30- 3.80 (m, 4 H), 4.10 (m, 1 H), 4.40 (m, 4 H), 4.95 (m, 1H) 6.95- 7.10 (bs, 5 H), and 7.12- 7.20 10 ppm (bs, 5 H).

3 (S)-{2-[4-Benzyl-7-oxo-6(S)-(N-benzylxycarbonylamino)-[1,4]diazepan-1-yl]- 15 acetylamino}-4-oxo-butrylic acid trifluoroacetic acid salt (114b) was prepared from 109b by a similar method described for the synthesis of 114a to give 85 mg of viscous oil: ^1H NMR (500 MHz, CD₃OD) δ 1.20 (d, J = 7 Hz, 3 H), 2.28 (m, 2 H), 2.60 (m, 2 H), 3.18 (bs, 6 H), 3.35- 3.45 (m, 2 H), 3.60- 3.95 (m, 2 H), 4.15 (m, 1 H), 4.32 (m, 1 H), 4.42 (m, 1 H), 5.00 (bm, 2 H), 7.20 (bs, 5 H), and 7.40 ppm (bs, 5 H); ^{19}F NMR (470 MHz, CD₃OD) δ -10.72 ppm (s, 3 F).

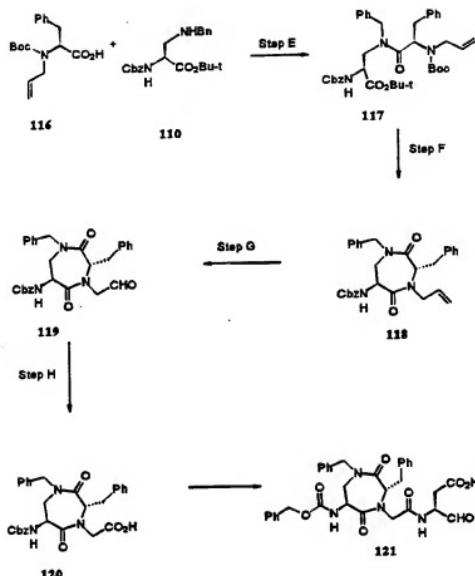
4-Oxo-3 (S)-{2(R,S)-[7-oxo-4-(3-phenyl-propionyl)- 25 6(S)-(3-phenyl-propionylamino)-[1,4]diazepan-1-yl]- propionylamino}-butrylic acid (115):
Step D. A suspension of 2(R,S)-[4-benzyl-7-oxo- 30 6(S)-(N-benzylxycarbonylamino)-[1,4]diazepan-1-yl]- propionic acid methyl ester (112b; 0.22 g, 0.49 mmol) and 20% Pd(OH)₂ on carbon (50 mg) in ethanol was stirred under hydrogen atmosphere for 7 hours. The solvent was evaporated under reduced pressure and the

- 260 -

residue dissolved in dichloromethane (20 mL) then
treated with triethylamine (1 mL) and
dihydrocinnamoyl chloride (170 mg, 1 mmol). The
resulting mixture was allowed to stir overnight then
5 diluted with ethyl acetate and washed with 1 N NaOH.
The organic layer was dried (MgSO_4), filtered and
evaporated to give an oil. Chromatography (silica-
gel, 4:1 hexane: ethyl acetate) gave 0.175 g (75%
yield) of 113 as an oil.

10 Step C. A 0.15 g sample of 113 (0.32 mmol) was
dissolved in methanol, treated with 1 M LiOH (0.32
mL), stirred at 40 °C overnight then evaporated to
dryness. The residue was azeotroped with ethanol (2
x 10 mL), acetonitrile (2 x 10 mL), benzene (2 x 10
15 mL) then dried under vacuum. The resulting residue
was converted to 115 by a method similar to that
described in example 3, compound K (steps A, B, and
C).

- 261 -



3-[2-[2,4-Dibenzyl-3,7-dioxo-6-(N-benzyloxycarbonylamino)-[1,4]diazepan-1-yl]-acetylaminomethyl]-4-oxo-butyric acid (121):

5 **Step E.** A solution of tert-butyl-2-N-carbobenzoxy-3-N-benzyl-(S)-2,3-diaminopropionate (110; 1.77 g, 4.6 mmol), N-allyl-N-tert-butoxycarbonyl-(S)-phenylalanine (116; 1.04 g, 4.8 mmol), HOBT (0.74 g, 5.5 mmol) and EDC (1.33 g, 6.9 mmol) in dichloromethane (50 mL) was allowed to stir at 25 °C for 16 h then diluted with dichloromethane (100 mL) and washed with water. The organic layer was dried (MgSO_4), filtered and evaporated to give an oil. Chromatography (silica-gel, 85: 15 hexane: ethyl

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- 262 -

acetate) gave 1.34 g (43% yield) of 117 as a colorless viscous oil.

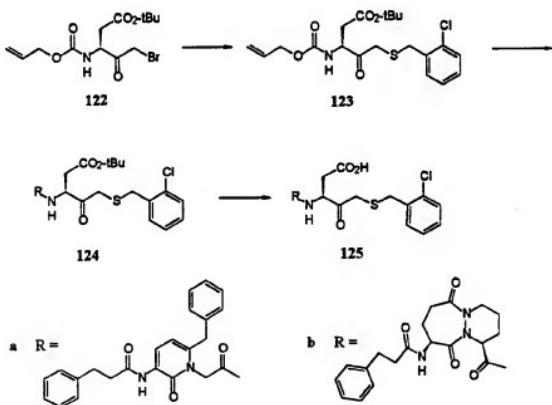
Step F. A 1.34 g sample of 117 was dissolved in dichloromethane (3 mL) and treated with a 50% 5 solution of trifluoroacetic acid in dichloromethane (20 mL). After 1.5 h, the solvent was removed under reduced pressure and the residue dried under vacuum then dissolved in dichloromethane (50 mL) and combined with 4-methylmorpholine (0.2 mL, 2 mmol), 10 HOBt (0.27 g, 2 mmol) and EDC (0.8 g, 4 mmol). The mixture was stirred overnight at 25 °C then diluted with dichloromethane and washed with water. The organic layer was dried (MgSO_4), filtered and evaporated to give an oil. Chromatography (silica- 15 gel, 7:3 hexane: ethyl acetate) gave 0.8 g (80% yield) of 118 as a viscous oil.

Step G. A 0.8 g sample of 118 was dissolved in methanol (40 mL), cooled to -78 °C and saturated with ozone until the solution was blue in color. The 20 excess ozone was removed by purging with argon then dimethylsulfide (5 mL) was added and the mixture allowed to warm to 25 °C and stir 3 h. Solvent removal and chromatography (silica-gel, 1:1 hexane: ethyl acetate) gave 0.74 g (74% yield) of 119 as a white solid.

Step H. A 0.2 g sample (0.4 mmol) of 119 was 25 dissolved in acetone (25 mL), cooled to 0 °C and treated dropwise with a solution of Jones reagent until the orange color persisted. 2-Propanol (5 mL) was then added to the mixture and the resulting soltuion filtered through Celite and washed with acetone. Solvent removal gave a green-white solid 30 that was dried under vacuum to give 120. The resulting residue was converted to 121 by a method

- 263 -

similar to that described in example 3, compound K (steps A, B, and C). Chromatography (SiO_2 , 95: 4.5: 0.5 dicholormethane: methanol: acetic acid eluent) gave 85 mg (53% yield) of cream colored solid which was identified as 3-[2-[2,4-dibenzyl-3,7-dioxo-6-(N-benzyloxycarbonylamino)-[1,4]diazepan-1-yl-acetylamino]-4-oxo-butrylic acid (121) on the basis of the following spectral data: ^1H NMR (500 MHz, CD_3OD) δ 2.38 (m, 1 H), 2.45 (m, 1 H), 3.21 (bs, 2 H), 3.32- 10 3.39 (bm, 6 H), 3.85 (m, 1 H), 4.05 (m, 1 H), 4.21 (bm, 1 H), 4.31 (bs, 1 H), 4.45 (dm, $J = 11$ Hz, 1 H), 4.95 (bs, 4 H), 7.20 (bs, 5 H), and 7.33- 7.45 ppm (m, 5 H); ^{19}F NMR (470 MHz, CD_3OD) δ -10.62 ppm (s, 3 F).



15 t-Butyl (3*S*) N-(allyloxycarbonyl)-3-amino-5-(2-chlorophenylmethylthio)-4-oxo-pentanoate (123). Potassium fluoride (273mg, 4.70mmol) and then 2-chlorophenylmethyl thiol (373mg, 2.35mmol) were added

- 264 -

to a stirred solution of (3S) t-butyl N-
(allyloxycarbonyl)-3-amino-5-bromo-4-oxo-pentanoate
(122; 749mg, 2.14mmol; WO 93 16710) in
dimethylformamide (20ml). The mixture was stirred
5 for 3.5h, quenched with water (50ml) and extracted
with ethyl acetate (2 x 50ml). The combined organic
extracts were washed with water (4 x 50ml) then brine
(50ml). They were dried ($MgSO_4$) and concentrated to
afford an oil which was purified by flash
10 chromatography (10-35% ethyl acetate / hexane) to
afford 832 mg (91%) of a colourless solid: mp. 45-6
 $^{\circ}C$; $[\alpha]_D^{20}$ -19.0° (c 1.0, CH_2Cl_2); IR (film) 3340,
2980, 2935, 1725, 1712, 1511, 1503, 1474, 1446, 1421,
1393, 1368, 1281, 1244, 1157, 1052, 1040, 995, 764,
15 739; 1H NMR ($CDCl_3$) δ 7.36 (2H, m), 7.21 (2H, m),
5.91 (2H, m), 5.27 (2H, m), 4.76 (1H, m), 4.59 (2H,
d), 3.78 (2H, s), 3.36 (2H, m), 2.91 (1H, dd), 2.74
(1H, dd), 1.43 (9H, s). Anal. Calcd for $C_{20}H_{26}ClNO_3S$:
C, 56.13; H, 6.12; N, 3.27; S, 7.49. Found: C,
20 56.08; H, 6.11; N, 3.26; S, 7.54. MS (C.I.) 430/28
($M^+ + 1$, 3%), 374/2 (100).

t-Butyl (3S) 3-(2(6-benzyl-1,2-dihydro-2-oxo-3-(3-
phenylpropionylamino)-1-pyridyl)acetylamino-5-(2-
chlorophenylmethylthio)-4-oxopentanoate (124a). 6-
25 Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionylamino)-
pyridyl acetic acid (52b; 300mg, 0.76mmol) in THF
(7ml) was stirred with 1-hydroxybenzotriazole (205mg,
1.52mmol) and 1-(3-dimethylaminopropyl-3-
ethylcarbodiimide hydrochloride). After 3 min, water
30 (12 drops) was added and the mixture stirred 10min
then treated with t-butyl (3S) N-(allyloxycarbonyl)-
3-amino-5-(2-chlorophenylmethylthio)-4-oxopentanoate

- 265 -

(123) (325mg, 0.76mmol), bis (triphenylphosphine) palladium II chloride (20mg) and tributyltin hydride (0.6ml, 2.28mmol). The mixture was stirred for 5h at room temperature, poured into ethyl acetate and washed with aqueous 1M HCl (x2), aqueous sodium bicarbonate, brine, dried ($MgSO_4$) and concentrated. The residue was triturated with pentane and the supernatant discarded. Chromatography (silica gel, 50% ethyl acetate/hexane) afforded a colourless foam (439mg, 81%): $[\alpha]_D^{21} -18.3^\circ$ (c 0.5, CH_2Cl_2); IR (KBr) 3356, 3311, 1722, 1689, 1646, 1599, 1567, 1513, 1367, 1154; 1H NMR ($CDCl_3$) δ 8.39 (1H, d), 8.23 (1H, s), 7.24 (14H, m), 6.16 (1H, d), 4.95 (1H, m), 4.63 (2H, m), 4.02 (2H, s), 3.74 (2H, s), 3.27 (2H, s), 2.85 (6H, m), 1.40 (9H, s). Anal. Calcd for $C_{39}H_{42}ClN_3O_6S$: C, 65.39; H, 5.91; N, 5.87. Found: C, 65.51; H, 5.99; N, 5.77.

t-Butyl [3S(1S,9S)]-3-(6,10-dioxo-1,2,3,4,7,8,9,10-octahydro)-9-(3-phenylpropionylamino)-6H-pyridazine[1,2-a][1,2]diazepine-1-carboxamido-5-(2-chlorophenylmethylthio)-4-oxopentanoate (124b) was prepared by a similar method as 124a from the thioether 123 and 3S(1S,9S)-3-(6,10-dioxo-1,2,3,4,7,8,9,10-octahydro)-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid (45a) to afford 452mg (50%) of colourless foam: mp 55-7 °C; $[\alpha]_D^{22} - 94.0^\circ$ (c 0.12, CH_2Cl_2); IR (KBr) 3288, 2934, 1741, 1722, 1686, 1666, 1644, 1523, 1433, 1260, 1225, 1146, 757; 1H NMR ($CDCl_3$) δ 7.35 (3H, m), 7.20 (7H, m), 6.46 (1H, d), 5.21 (1H, m), 4.97 (2H, m), 4.56 (1H, m), 3.75 (2H, s), 3.25 (3H, m), 2.93 (5H, m), 2.71 (1H,

- 266 -

dd), 2.55 (2H, m), 2.30 (1H, m), 1.92 (3H, m), 1.66 (2H, m), 1.42 (9H, s). Anal. Calcd for C₃₅H₄₃ClN₄O₂S. 0.25H₂O: C, 59.73; H, 6.23; Cl, 5.04; N, 7.96; S, 4.56. Found: C, 59.73; H, 6.19; Cl, 5.10; N, 7.79; S, 4.58. MS (-FAB) 697 (M-1, 100).

(3S)-3-(2-(6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionylamino)-1-pyridyl)acetylamino-5-(2-chlorophenylmethylthio)-4-oxopentanoic acid (125a). t-Butyl-3-(2-(6-benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionylamino)-1-pyridyl)acetyl-amino-5-(2-chlorophenylmethylthio)-4-oxopentanoate (124a) (400mg, 0.56mmol) in dichloromethane (3ml) at 0 °C was treated with trifluoroacetic acid (3ml) and stirred at 0 °C for 1h and room temperature for 0.5h. The solution was concentrated then redissolved in dichloromethane and reconcentrated. This procedure was repeated three times. The residue was stirred in ether for 1hr and filtered to yield a colourless solid (364mg, 99%):
mp. 165-7 °C; [α]_D²² -27.7 ° (c 0.2, CH₂Cl₂); IR (KBr) 3289, 1712, 1682, 1657, 1645, 1593, 1562, 1527, 1497, 1416, 1203, 1182; ¹H NMR (CDCl₃) δ 8.47 (1H, d), 8.21 (1H, s), 7.70 (1H, d), 7.22 (14H, m), 6.24 (1H, d), 5.03 (1H, m), 4.65 (2H, m), 4.06 (2H, s), 3.69 (2H, m), 3.23 (2H, m), 2.88 (6H, m).

[3S(1S, 9S)]-3-(6,10-dioxo-1,2,3,4,7,8,9,10-octahydro)-9-(3-phenylpropionylamino)-6H-pyridazine[1,2-a][1,2]diazepine-1-carboxamido-5-(2-chlorophenyl-methylthio)-4-oxopentanoic acid (125b), was prepared by a similar method as 125a from the t-butyl ester 124b to afford

- 267 -

362mg (93%) of colourless powder: mp 76-80 °C; $[\alpha]_D^{25}$
-134 ° (c 0.10, MeOH); IR (KBr) 3309, 2935, 1725,
1658, 1528, 1445, 1417, 1277, 1219, 1175; ^1H NMR (D_6 -
DMSO) δ 8.80 (1H, d), 8.19 (1H, d), 7.31 (9H, m),
5.09 (1H, m), 4.74 (1H, m), 4.63 (1H, m), 4.35 (1H,
m), 3.76 (2H, m), 3.28 (3H, m), 2.80 (5H, m), 2.52
(4H, m), 2.16 (2H, m), 1.90 (3H, m). Anal. Calcd for
 $\text{C}_{31}\text{H}_{35}\text{Cl}_2\text{N}_2\text{O}_5\text{S}$. 0.25H₂O: C, 57.49; H, 5.53; N, 8.65; S,
4.95. Found: C, 57.35; H, 5.43; N, 8.45; S, 4.88.
10 MS (-FAB) 641 (M-1, 100).

The data of the examples above demonstrate
that compounds according to this invention display
inhibitory activity towards IL-1 β Converting Enzyme.
15 Insofar as the compounds of this invention
are able to inhibit ICE in vitro and furthermore, may
be delivered orally to mammals, they are of evident
clinical utility for the treatment of IL-1 mediated
diseases. These tests are predictive of the
20 compounds ability to inhibit ICE *in vivo*.

While we have described a number of
embodiments of this invention, it is apparent that
our basic constructions may be altered to provide
other embodiments which utilize the products and
25 processes of this invention. Therefore, it will be
appreciated that the scope of this invention is to be
defined by the appended claims, rather than by the
specific embodiments which have been presented by way
of example.

CLAIMS

We claim:

1. An ICE inhibitor comprising:
 - (a) a first and a second hydrogen bonding moiety, each of said moieties being capable of forming a hydrogen bond with a different backbone atom of ICE, said backbone atom being selected from the group consisting of the carbonyl oxygen of Arg-341, the amide -NH- group of Arg-341, the carbonyl oxygen of Ser-339 and the amide -NH- group of Ser-339;
 - (b) a first and a second moderately hydrophobic moiety, said moieties each being capable of associating with a separate binding pocket of ICE when the inhibitor is bound thereto, said binding pocket being selected from the group consisting of the P2 binding pocket, the P3 binding pocket, the P4 binding pocket and the P' binding pocket; and
 - (c) an electronegative moiety comprising one or more electronegative atoms, said atoms being attached to the same atom or to adjacent atoms in the moiety and said moiety being capable of forming one or more hydrogen bonds or salt bridges with residues in the P1 binding pocket of ICE.
- 25 2. The ICE inhibitor according to claim 1, wherein said inhibitor is characterized by a neutral or favorable enthalpic contribution from the sum of all electrostatic interactions between the inhibitor and ICE when the inhibitor is bound thereto.
- 30 3. The ICE inhibitor according to claim 1, wherein said inhibitor has a molecular weight less than or equal to about 700 Daltons.

- 269 -

4. The ICE inhibitor according to claim 3,
wherein said inhibitor has a molecular weight between
about 400 and about 600 Daltons.

5 5. The ICE inhibitor according to claim 1,
wherein said inhibitor further comprises less than
two secondary amide bonds.

10 6. The ICE inhibitor according to claim 1,
wherein said inhibitor further comprises less than
two groups selected from the set consisting of
secondary amide groups and carbamate groups.

15 7. The ICE inhibitor according to claim 1,
wherein said inhibitor further comprises a
polysubstituted cyclic group having between three and
seven substituents, said cyclic group not comprising
the first or second moderately hydrophobic moiety or
the electronegative moiety.

20 8. The ICE inhibitor according to claim 1
or 7, wherein said inhibitor is characterized by a
strain energy of binding of said inhibitor to ICE
less than or equal to about 10 kcal/mole.

9. The ICE inhibitor according to claim 1
or 7, wherein when said inhibitor is bound to ICE at
least two of the following four conditions 1) through
4) are met:

- 25 1) one of said moderately hydrophobic
moieties associates with the P2 binding pocket of
ICE, in such a way that:
a) the distance from the center of
mass of the moderately hydrophobic moiety in the P2

- 270 -

binding pocket to the carbonyl oxygen of Arg-341' of ICE is between about 7.1Å and about 12.5Å;

5 b) the distance from the center of mass of the moderately hydrophobic moiety in the P2 binding pocket to the amide nitrogen of Arg-341 of ICE is between about 6.0Å and about 12Å; and

10 c) the distance from the center of mass of the moderately hydrophobic moiety in the P2 binding pocket to the carbonyl oxygen of Ser-339 of ICE is between about 3.7Å and about 9.5Å;

2) one of said moderately hydrophobic moieties associates with the P3 binding pocket of ICE in such a way that:

15 a) the distance from the center of mass of the moderately hydrophobic moiety in the P3 binding pocket to the carbonyl oxygen of Arg-341 of ICE is between about 3.9Å and about 9.5Å;

20 b) the distance from the center of mass of the moderately hydrophobic moiety in the P3 binding pocket to the amide nitrogen of Arg-341 of ICE is between about 5.4Å and about 11Å; and

25 c) the distance from the center of mass of the moderately hydrophobic moiety in the P3 binding pocket to the carbonyl oxygen of Ser-339 of ICE is between about 7.0Å and about 13Å;

3) one of said moderately hydrophobic moieties associates with the P4 binding pocket of ICE in such a way that:

30 a) the distance from the center of mass of the moderately hydrophobic moiety in the P4 binding pocket to the carbonyl oxygen of Arg-341 of ICE is between about 4.5Å and about 7.5Å;

b) the distance from the center of mass of the moderately hydrophobic moiety in the P4

- 271 -

binding pocket to the amide nitrogen of Arg-341 of ICE is between about 5.5Å and about 8.5Å; and

5 c) the distance from the center of mass of the moderately hydrophobic moiety in the P4 binding pocket to the carbonyl oxygen of Ser-339 of ICE is between about 8Å and about 11Å; and

4) one of said moderately hydrophobic moieties associates with the P' binding pocket of ICE in such a way that:

10 a) the distance from the center of mass of the moderately hydrophobic moiety in the P' binding pocket to the carbonyl oxygen of Arg-341 of ICE is between about 11Å and about 16Å;

15 b) the distance from the center of mass of the moderately hydrophobic moiety in the P' binding pocket to the amide nitrogen of Arg-341 of ICE is between about 10Å and about 15Å; and

c) the distance from the center of mass of the moderately hydrophobic moiety in the P' binding pocket to the carbonyl oxygen of Ser-339 of ICE is between about 8Å and about 12Å.

10. The ICE inhibitor according to claim 1 or 7, wherein when said inhibitor is bound to ICE, said moderately hydrophobic moieties separately associate with the P' binding pocket of ICE and the P2 binding pocket of ICE and the distance from the center of mass of the moderately hydrophobic moiety in the P' binding pocket to the center of mass of the moderately hydrophobic moiety in the P2 binding pocket is between about 6.5Å and about 13Å.

11. The ICE inhibitor according to claim 1 or 7, wherein when said inhibitor is bound to ICE,

- 272 -

5 said moderately hydrophobic moieties separately
associate with the P' binding pocket of ICE and the
P3 binding pocket of ICE and the distance from the
center of mass of the moderately hydrophobic moiety
in the P' binding pocket to the center of mass of the
moderately hydrophobic moiety in the P3 binding
pocket is between about 6Å and about 15Å.

10 12. The ICE inhibitor according to claim 1
or 7, wherein when said inhibitor is bound to ICE,
said moderately hydrophobic moieties separately
associate with the P' binding pocket of ICE and the
P4 binding pocket of ICE and the distance from the
center of mass of the moderately hydrophobic moiety
in the P' binding pocket to the center of mass of the
moderately hydrophobic moiety in the P4 binding
pocket is between about 14Å and about 22Å.

20 13. The ICE inhibitor according to claim 1
or 7, wherein when said inhibitor is bound to ICE,
said moderately hydrophobic moieties separately
associate with the P2 binding pocket of ICE and the
P3 binding pocket of ICE and the distance from the
center of mass of the moderately hydrophobic moiety
in the P2 binding pocket to the center of mass of the
moderately hydrophobic moiety in the P3 binding
pocket is between about 5.5Å and about 13Å.

25 14. The ICE inhibitor according to claim 1
or 7, wherein when said inhibitor is bound to ICE,
said moderately hydrophobic moieties separately
associate with the P2 binding pocket of ICE and the
P4 binding pocket of ICE and the distance from the
center of mass of the moderately hydrophobic moiety

- 273 -

in the P2 binding pocket to the center of mass of the moderately hydrophobic moiety in the P4 binding pocket is between about 9Å and about 17Å.

15. The ICE inhibitor according to claim 1
5 or 7, wherein when said inhibitor is bound to ICE,
said moderately hydrophobic moieties separately
associate with the P3 binding pocket of ICE and the
P4 binding pocket of ICE and the distance from the
center of mass of the moderately hydrophobic moiety
in the P3 binding pocket to the center of mass of the
moderately hydrophobic moiety in the P4 binding
pocket is between about 7.5Å and about 17Å.

16. The ICE inhibitor according to claim 1
15 or 7, wherein when said inhibitor is bound to ICE,
said first hydrogen bonding moiety forms a hydrogen
bond with the carbonyl oxygen of Ser-339 of ICE and
said second hydrogen bonding moiety forms a hydrogen
bond with the carbonyl oxygen of Arg-341 of ICE and
wherein the distance between said hydrogen bonding
moieties is between about 5Å and about 7.5Å.

17. The ICE inhibitor according to claim 1
or 7, wherein when said inhibitor is bound to ICE,
said first hydrogen bonding moiety forms a hydrogen
bond with the carbonyl oxygen of Ser-339 of ICE and
said second hydrogen bonding moiety forms a hydrogen
bond with the amide -NH- group of Arg-341 of ICE and
wherein the distance between said moieties is between
about 2.5Å and about 5Å.

30 18. The ICE inhibitor according to claim 1
or 7, wherein when said inhibitor is bound to ICE,

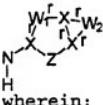
- 274 -

said first hydrogen bonding moiety forms a hydrogen bond with the carbonyl oxygen of Arg-341 of ICE and said second hydrogen bonding moiety forms a hydrogen bond with the amide -NH- group of Arg-341 of ICE and
5 wherein the distance between said hydrogen bonding moieties is between about 2.5 Å and about 4 Å.

19. An ICE inhibitor comprising:

(a) a scaffold of formula I:

(I)



wherein:

each X is independently C or N;

Z is CO or SO₂;

15 W₁ is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different X atoms through bonds r;

20 W₂ is a straight chain comprising 3-5 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different X atoms through bonds r;

each bond labeled r is independently a single or a double bond;

30 H is a first hydrogen bonding moiety and Z is a second hydrogen bonding moiety, each of said moieties being capable of forming a hydrogen

- 275 -

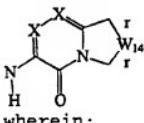
bond with a different backbone atom of ICE, said backbone atom being selected from the group consisting of the carbonyl oxygen of Arg-341, the amide -NH- group of Arg-341, the carbonyl oxygen of Ser-339 and the amide -NH- group of Ser-339;

5 (b) a first and a second moderately hydrophobic moiety, said moieties each being covalently bound to said scaffold and each being capable of associating with a separate binding 10 pocket of ICE when the inhibitor is bound thereto, said binding pocket being selected from the group consisting of the P2 binding pocket, the P3 binding pocket, the P4 binding pocket and the P' binding pocket; and

15 (c) an electronegative moiety comprising one or more electronegative atoms, said atoms being attached to the same atom or to adjacent atoms in the moiety and said moiety being covalently bound to said scaffold and being capable of forming 20 one or more hydrogen bonds or salt bridges with residues in the P1 binding pocket of ICE.

20. The ICE inhibitor according to claim 19, wherein said scaffold has the formula:

(IA)



wherein:

25 each X is independently C or N;

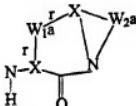
W₁₄ is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or

- 276 -

unsaturated and said chain comprising two ends which
are covalently bound to two different C atoms through
bonds r; and
each bond labeled r is independently a single or a
5 double bond.

21. The ICE inhibitor according to claim 19,
wherein said scaffold has the formula:

(IB)



wherein:

10 X is C or N;

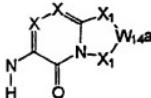
W_{1a} is a straight chain comprising 1-3
covalently bound members independently selected from
the group consisting of C, N, S and O, said covalent
bonds between said members being independently
15 saturated or unsaturated and said chain comprising
two ends which are covalently bound to two different
X atoms through bonds r;

20 W_{2a} is a straight chain comprising 3-4
covalently bound members independently selected from
the group consisting of C, N, S and O, said chain
comprising two ends which are covalently bound to two
different atoms to form an aryl or heteroaromatic
ring therewith; and

25 each bond labeled r is independently a
single or a double bond.

22. The ICE inhibitor according to claim 19,
wherein said scaffold has the formula:

(IC)



wherein:

- 5 each X is independently C or N;
 each X₁ is independently C, N, or O; and
 W_{14a} is a straight chain comprising 1-3
 10 covalently bound members independently selected from
 the group consisting of C, N, S and O, said covalent
 bonds between said members being saturated or
 unsaturated and said chain comprising two ends which
 are covalently bound to two different X₁ atoms to
 form a non-aromatic ring therewith.

15 23. An ICE inhibitor comprising:
 a scaffold of formula II:

(II)



wherein:

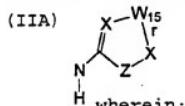
- 20 each X is independently C or N;
 Z is CO or SO₂;
 W₃ is a straight chain comprising 2-4
 covalently bound members independently selected from
 the group consisting of C, N, S and O, said covalent
 bonds between said members being independently
 saturated or unsaturated and said chain comprising
 25 two ends which are covalently bound to two different
 X atoms through bonds r;
 each bond labeled r is independently a
 single or a double bond;

H is a first hydrogen bonding moiety and Z is a second hydrogen bonding moiety, each of said moieties being capable of forming a hydrogen bond with a different backbone atom of ICE, said backbone atom being selected from the group consisting of the carbonyl oxygen of Arg-341, the amide -NH- group of Arg-341, the carbonyl oxygen of Ser-339 and the amide -NH- group of Ser-339;

(a) a first and a second moderately hydrophobic moiety, said moieties each being covalently bound to said scaffold and each being capable of associating with a separate binding pocket of ICE when the inhibitor is bound thereto, said binding pocket being selected from the group consisting of the P2 binding pocket, the P3 binding pocket, the P4 binding pocket and the P' binding pocket; and

(b) an electronegative moiety comprising one or more electronegative atoms, said atoms being attached to the same atom or to adjacent atoms in the moiety and said moiety being covalently bound to said scaffold and being capable of forming one or more hydrogen bonds or salt bridges with residues in the P1 binding pocket of ICE.

24. The ICE inhibitor according to claim 23, wherein said scaffold has the formula:



each X is independently C or N;
Z is CO or SO₂;

- 279 -

W₁₅ is a straight chain comprising 1-2 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different X atoms; and

the bond labeled r is a single or a double bond.

10

25. The ICE inhibitor according to claim 23, wherein said scaffold has the formula:

(IIB)



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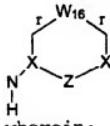
wherein:

each X is independently C or N; and
Z is CO or SO₂.

20

26. The ICE inhibitor according to claim 23, wherein said scaffold has the formula:

(IIC)



wherein:

each X is independently C or N;
Z is CO or SO₂;

25

W₁₆ is a straight chain comprising 1-2 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising

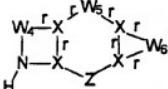
- 280 -

two ends which are covalently bound to two different C atoms through bonds r; and
 each bond labeled r is independently a single or a double bond.

5 27. An ICE inhibitor comprising:

(a) a scaffold of formula III:

(III)



, wherein:

10 each X is independently C or N;

Z is CO or SO₂;

15 W₄ is a straight chain comprising 2-4 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different atoms;

20 W₅ is a direct bond or a straight chain comprising 1-2 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different X atoms through bonds r;

25 W₆ is a straight chain comprising 3-5 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different X atoms through bonds r;

- 281 -

each bond labeled r is independently a single or a double bond;

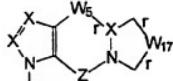
H is a first hydrogen bonding moiety and Z is a second hydrogen bonding moiety, each of said moieties being capable of forming a hydrogen bond with a different backbone atom of ICE, said backbone atom being selected from the group consisting of the carbonyl oxygen of Arg-341, the amide -NH- group of Arg-341, the carbonyl oxygen of Ser-339 and the amide -NH- group of Ser-339;

(b) a first and a second moderately hydrophobic moiety, said moieties each being covalently bound to said scaffold and each being capable of associating with a separate binding pocket of ICE when the inhibitor is bound thereto, said binding pocket being selected from the group consisting of the P2 binding pocket, the P3 binding pocket, the P4 binding pocket and the P' binding pocket; and

(c) an electronegative moiety comprising one or more electronegative atoms, said atoms being attached to the same atom or to adjacent atoms in the moiety and said moiety being covalently bound to said scaffold and being capable of forming one or more hydrogen bonds or salt bridges with residues in the P1 binding pocket of ICE.

28. The ICE inhibitor according to claim 27, wherein said scaffold has the formula:

(IIIA)



30 wherein:

- 282 -

each X is independently C or N;

Z is CO or SO₂;

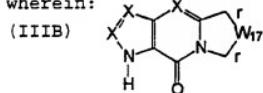
W₅ is a direct bond or a straight chain comprising 1-2 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different atoms;

W₁, is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different C atoms through bonds r; and

each bond labeled r is independently a single or a double bond.

29. The ICE inhibitor according to claim 27,

wherein:



wherein:

each X is independently C or N;

W₁₇ is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different C atoms through bonds r; and

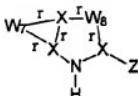
each bond labeled r is independently a

single or a double bond.

30. An ICE inhibitor comprising:

(a) a scaffold of formula IV:

(IV)



5

wherein:

each X is independently C or N;

Z is CO or SO₂;

10 W₁ is a straight chain comprising 3-5 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different X atoms through bonds r;

15 W₂ is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated, and said chain comprising two ends which are covalently bound to two different X atoms through bonds r;

each bond labeled r is independently a single or a double bond;

25 H is a first hydrogen bonding moiety and Z is a second hydrogen bonding moiety, each of said moieties being capable of forming a hydrogen bond with a different backbone atom of ICE, said backbone atom being selected from the group consisting of the carbonyl oxygen of Arg-341, the amide -NH- group of Arg-341, the carbonyl oxygen of Ser-339 and the amide

30

- 284 -

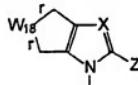
-NH- group of Ser-339;

(b) a first and a second moderately hydrophobic moiety, said moieties each being covalently bound to said scaffold and each being capable of associating with a separate binding pocket of ICE when the inhibitor is bound thereto, said binding pocket being selected from the group consisting of the P2 binding pocket, the P3 binding pocket, the P4 binding pocket and the P' binding pocket; and

(c) an electronegative moiety comprising one or more electronegative atoms, said atoms being attached to the same atom or to adjacent atoms in the moiety and said moiety being covalently bound to said scaffold and being capable of forming one or more hydrogen bonds or salt bridges with residues in the P1 binding pocket of ICE.

31. The ICE inhibitor according to claim 30, wherein said scaffold has the formula:

20 (IVA)



wherein:

each X is independently C or N;

Z is CO or SO₂;

25 W₁₈ is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different C atoms through bonds r; and

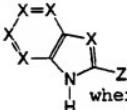
30 each bond labeled r is independently a

- 285 -

single or a double bond.

32. The ICE inhibitor according to claim 30,
wherein said scaffold has the formula:

(IVB)



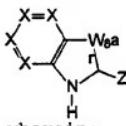
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wherein:
each X is independently C or N; and
Z is CO or SO₂.

33. The ICE inhibitor according to claim 30,
wherein said scaffold has the formula:

10

(IVC)



wherein:

each X is independently C or N;

Z is CO or SO₂;

15

W_s is a straight chain comprising 1-3

covalently bound members independently selected from

the group consisting of C, N, S and O, said covalent
bonds between said members being independently
saturated or unsaturated and said chain comprising
two ends which are covalently bound to two different

20

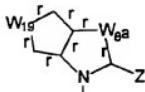
C atoms; and

the bond labeled r is a single or a
double bond.

- 286 -

34. The ICE inhibitor according to claim 30,
wherein said scaffold has the formula:

(IVD)



wherein:

5 Z is CO or SO₂;

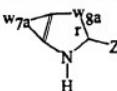
W_{6a} is a straight chain comprising 1-3
covalently bound members independently selected from
the group consisting of C, N, S and O, said covalent
bonds between said members being independently
10 saturated or unsaturated and said chain comprising
two ends which are covalently bound to two different
C atoms through bonds r;

W_{1g} is a straight chain comprising 1-3
covalently bound members independently selected from
15 the group consisting of C, N, S and O, said covalent
bonds between said members being independently
saturated or unsaturated and said chain comprising
two ends which are covalently bound to two different
C atoms through bonds r; and

20 each bond labeled r is independently a
single or a double bond.

35. The ICE inhibitor according to claim 30,
wherein said scaffold has the formula:

(IVE)



wherein:

25 Z is CO or SO₂;

W_{8a} is a straight chain comprising 1-3
covalently bound members independently selected from

- 287 -

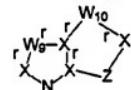
the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different C atoms;

5 W_9 is a straight chain comprising 3 covalently bound members independently selected from the group consisting of C, N, S and O, said chain comprising two ends which are covalently bound to two different C atoms to form an aryl ring therewith; and
10 the bond labeled r is a single or a double bond.

36. An ICE inhibitor comprising:

a) a scaffold of formula V:

15 (V)



wherein:

each X is independently C or N;

Z is CO or SO₂;

20 W_9 is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different X atoms through bonds r;

25 W_{10} is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising

- 288 -

two ends which are covalently bound to two different X atoms through bonds r;

each bond labeled r is independently a single or a double bond;

5 H is a first hydrogen bonding moiety and Z is a second hydrogen bonding moiety, each of said moieties being capable of forming a hydrogen bond with a different backbone atom of ICE, said backbone atom being selected from the group consisting of the carbonyl oxygen of Arg-341, the amide -NH- group of Arg-341, the carbonyl oxygen of Ser-339 and the amide -NH- group of Ser-339;

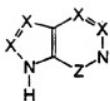
10 b) a first and a second moderately hydrophobic moiety, said moieties each being 15 covalently bound to said scaffold and each being capable of associating with a separate binding pocket of ICE when the inhibitor is bound thereto, said binding pocket being selected from the group consisting of the P2 binding pocket, the P3 binding 20 pocket, the P4 binding pocket and the P' binding pocket; and

25 c) an electronegative moiety comprising one or more electronegative atoms, said atoms being attached to the same atom or to adjacent atoms in the moiety and said moiety being covalently bound to said scaffold and being capable of forming one or more 30 hydrogen bonds or salt bridges with residues in the P1 binding pocket of ICE.

37. The ICE inhibitor according to claim 36, 30 wherein said scaffold has the formula:

- 289 -

(VA)



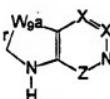
wherein:

each X is independently C or N; and

5 Z is CO or SO₂.

38. The ICE inhibitor according to claim 36,
wherein said scaffold has the formula:

(VB)



wherein:

each X is independently C or N;

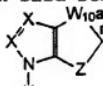
Z is CO or SO₂;

W_{9a} is a straight chain comprising 1-3
15 covalently bound members independently selected from
the group consisting of C, N, S and O, said covalent
bonds between said members being independently
saturated or unsaturated and said chain comprising
two ends which are covalently bound to two different
C atoms; and

20 the bond labeled r is a single or a
double bond.

39. The ICE inhibitor according to claim 36,
wherein said scaffold has the formula:

(VC)



wherein:

each X is independently C or N;

- 290 -

Z is CO or SO₂;

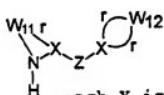
W_{10a} is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different X atoms; and

the bond labeled r is a single or a double bond.

40. An ICE inhibitor comprising:

(a) a scaffold of formula VI:

(VI)



wherein:

each X is independently C or N;
Z is CO or SO₂;

W₁₁ is a straight chain comprising 3-5 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different atoms to form a ring which may optionally be benzofused or pyridinofused;

W₁₂ is a straight chain comprising 4-6 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to the indicated X atom through bonds r;

each bond labeled r is independently a

- 291 -

single or a double bond;

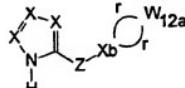
H is a first hydrogen bonding moiety and Z is a second hydrogen bonding moiety, each of said moieties being capable of forming a hydrogen bond with a different backbone atom of ICE, said backbone atom being selected from the group consisting of the carbonyl oxygen of Arg-341, the amide -NH- group of Arg-341, the carbonyl oxygen of Ser-339 and the amide -NH- group of Ser-339;

(b) a first and a second moderately hydrophobic moiety, said moieties each being covalently bound to said scaffold and each being capable of associating with a separate binding pocket of ICE when the inhibitor is bound thereto, said binding pocket being selected from the group consisting of the P2 binding pocket, the P3 binding pocket, the P4 binding pocket and the P' binding pocket; and

(c) an electronegative moiety comprising one or more electronegative atoms, said atoms being attached to the same atom or to adjacent atoms in the moiety and said moiety being covalently bound to said scaffold and being capable of forming one or more hydrogen bonds or salt bridges with residues in the P1 binding pocket of ICE.

41. The ICE inhibitor according to claim 40, wherein said scaffold has the formula:

(VIA)



wherein:

each X and X_b is independently C or N;

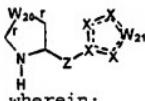
- 292 -

Z is CO or SO₂;

W_{12s} is a straight chain comprising 4-6
covalently bound members independently selected from
the group consisting of C, N, S and O, said covalent
bonds between said members being independently
5 saturated or unsaturated and said chain comprising
two ends which are covalently bound to the indicated
X_b atom through bonds r; and
each bond labeled r is independently a single
10 or a double bond.

42. The ICE inhibitor according to claim 40,
wherein said scaffold has the formula:

(VIB)



wherein:

15 each X is independently C or N;
Z is CO or SO₂;

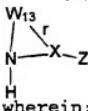
W₂₀ is a straight chain comprising 1-3
covalently bound members independently selected from
the group consisting of C, N, S and O, said covalent
bonds between said members being independently
20 saturated or unsaturated and said chain comprising
two ends which are covalently bound to two different
C atoms through bonds r;

W₂₁ is a straight chain comprising 1-2
25 covalently bound members independently selected from
the group consisting of C, N, S and O, said chain
comprising two ends which are covalently bound to two
different C atoms to form an aryl ring therewith; and
each bond labeled r is independently a
30 single or a double bond.

43. An ICE inhibitor comprising:

(a) a scaffold of formula VII:

(VII)



wherein:

5 X is C or N;

Z is CO or SO₂;10 W₁₃ is a straight chain comprising 3-5 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different atoms;

15 the bond labeled r is a single or a double bond;

20 H is a first hydrogen bonding moiety and Z is a second hydrogen bonding moiety, each of said moieties being capable of forming a hydrogen bond with a different backbone atom of ICE, said backbone atom being selected from the group consisting of the carbonyl oxygen of Arg-341, the amide -NH- group of Arg-341, the carbonyl oxygen of Ser-339 and the amide -NH- group of Ser-339;

25 (b) a first and a second moderately hydrophobic moiety, said moieties each being covalently bound to said scaffold and each being capable of associating with a separate binding pocket of ICE when the inhibitor is bound thereto, said binding pocket being selected from the group consisting of the P2 binding pocket, the P3 binding pocket, the P4 binding pocket and the P' binding pocket; and

- 294 -

5 (c) an electronegative moiety comprising one or more electronegative atoms, said atoms being attached to the same atom or to adjacent atoms in the moiety and said moiety being covalently bound to said scaffold and being capable of forming one or more hydrogen bonds or salt bridges with residues in the P1 binding pocket of ICE.

44. The ICE inhibitor according to claim 43, wherein said scaffold has the formula:

10 (VIIA)



wherein:

each X is independently C or N; and
Z is CO or SO₂.

15

45. The ICE inhibitor according to claim 43, wherein said scaffold has the formula:

(VIIB)



wherein:

X is C or N;
Z is CO or SO₂;

20

W₂₂ is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different atoms; and

25

the bond labeled r is a single or a double bond.

- 295 -

46. The ICE inhibitor according to claim 43,
wherein said scaffold has the formula:

(VIIC)



wherein:

5 X is C or N;

Z is CO or SO₂;

10 W₂₃ is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different atoms; and

15 the bond labeled r is a single or a double bond.

47. The ICE inhibitor according to claim 43,
wherein said scaffold has the formula:

(VIID)



20 wherein:

X is C or N;

Z is CO or SO₂;

25 W_{22a} is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different atoms through bonds r; and

- 296 -

each bond labeled r is independently a single or a double bond.

48. An ICE inhibitor comprising:

- a) a scaffold comprising any
5 monocyclic, bicyclic or tricyclic system, wherein each ring of said system comprises 5-7 members, said system comprising C, N, O or S, said system being aromatic or non-aromatic and comprising a central ring, wherein the distance between the centroid of said central ring and the alpha carbon of Cys-285 of ICE is between about 5.0Å and about 6.0Å when the inhibitor is bound to ICE and the distance between the centroid of said central ring and the alpha carbon of His-237 of ICE is between about 5.5Å and about 6.5Å when the inhibitor is bound to ICE;
- b) a first hydrogen bonding moiety and a second hydrogen bonding moiety, each of said
20 moieties being capable of forming a hydrogen bond with a different backbone atom of ICE, said atoms being selected from the group consisting of the carbonyl oxygen of Arg-341, the amide -NH- group of Arg-341, the carbonyl oxygen of Ser-339 and the amide -NH- group of Ser-339;
- c) a first and a second moderately
25 hydrophobic moiety, said moieties each being covalently bound to said scaffold and each being capable of associating with a separate binding pocket of ICE when the inhibitor is bound thereto, said binding pocket being selected from the group
30 consisting of the P2 binding pocket, the P3 binding pocket, the P4 binding pocket and the P' binding pocket; and
- d) an electronegative moiety

- 297 -

comprising one or more electronegative atoms, said atoms being attached to the same atom or to adjacent atoms in the moiety and said moiety being covalently bound to said scaffold and being capable of forming 5 one or more hydrogen bonds or salt bridges with residues in the P1 binding pocket of ICE.

49. A compound represented by the formula:



10 α X_1 is CH or N;

15 g is 0 or 1;

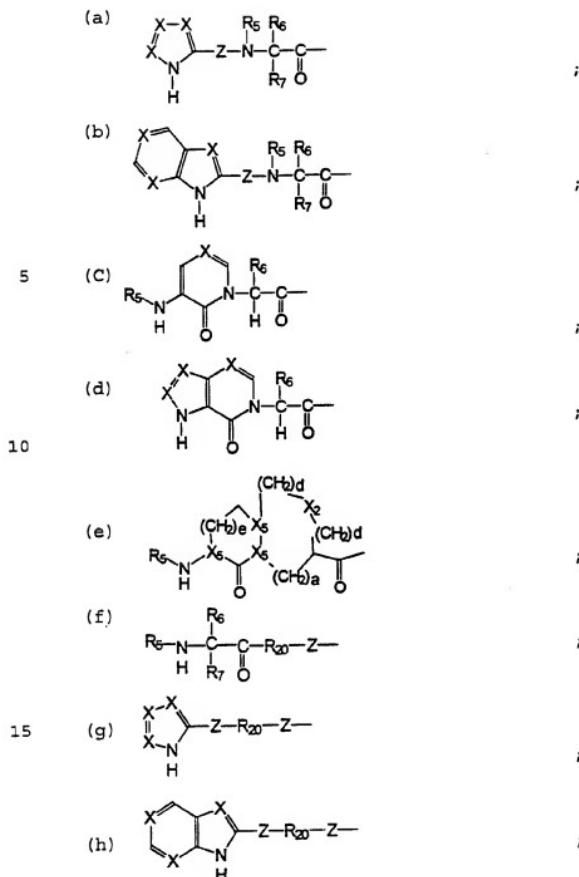
each J is independently selected from the group consisting of -H, -OH, and -F, provided that when a first and second J are bound to a C and said first J is -OH, said second J is -H;

20 m is 0, 1, or 2;

T is $-\text{Ar}_3$, $-\text{OH}$, $-\text{CF}_3$, $-\text{CO-CO}_2\text{H}$, $-\text{CO}_2\text{H}$ or any bioisosteric replacement for $-\text{CO}_2\text{H}$;

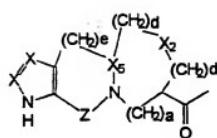
25 R_1 is selected from the group consisting of the following formulae, in which any ring may optionally be singly or multiply substituted at any carbon by Q_1 , at any nitrogen by R_5 , or at any atom by $=\text{O}$, $-\text{OH}$, $-\text{CO}_2\text{H}$, or halogen, and in which any saturated ring may optionally be unsaturated at one or two bonds:

- 298 -

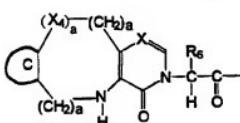


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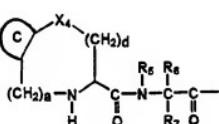
(i)



(j)

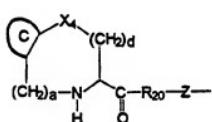


(k)



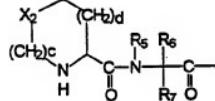
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(l)

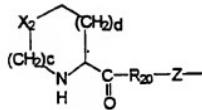


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(m)

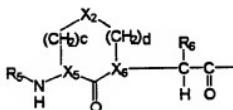


(n)



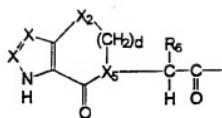
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(o)

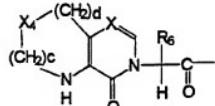


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(p)

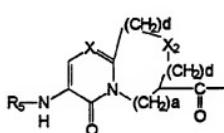


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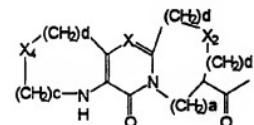


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(r)

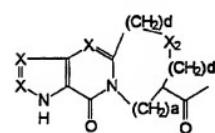


(s)



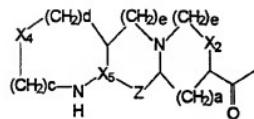
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(t)



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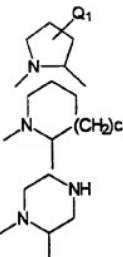
(v)



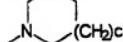
- 301 -

R₂₀ is selected from the group consisting of:

(aa1)



(aa2)



5

(aa3)



;

;

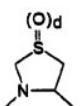
;

(aa4)



10

(aa5)



;

;

(bb)



;

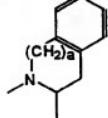
15

(cc)



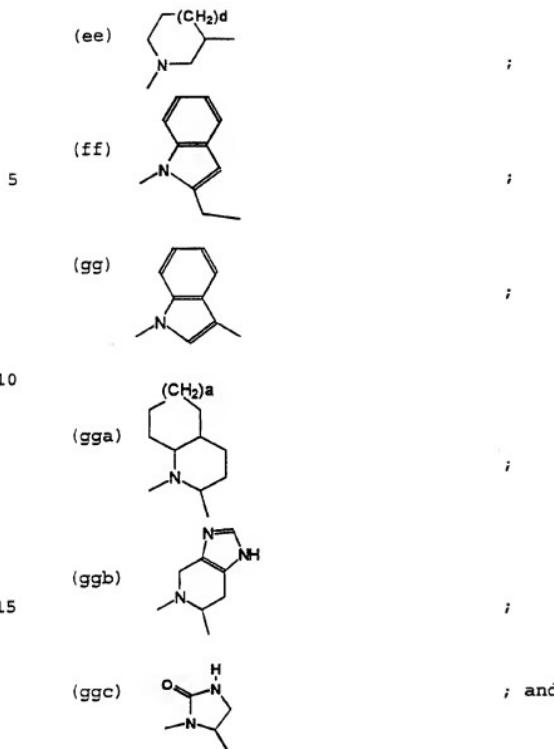
;

(dd)



;

- 302 -



20 wherein each ring C is independently chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

- 303 -

R₃ is
-CN,
-CH=CH-R₉,
-CH=N-O-R₉,
5 - (CH₂)₁₋₃-T₁-R₉,
-CJ₂-R₉,
-CO-R₁₃, or
-CO-CO-N₁₀
10 \ R₅
 \ R₁₀;

each R₄ is independently selected from the group consisting of:

-H,
-Ar₁,
15 -R₉,
-T₁-R₉, and
-(CH₂)_{1,2,3}-T₁-R₉,

each T₁ is independently selected from the group consisting of:

20 -CH=CH-,
-O-,
-S-,
-SO-,
-SO₂-,
25 -NR₁₀-,
-NR₁₀-CO-,
-CO-,
-O-CO-,
-CO-O-,
30 -CO-NR₁₀-,
-O-CO-NR₁₀-,
-NR₁₀-CO-O-,

-NR₁₀-CO-NR₁₀⁻,
-SO₂-NR₁₀⁻,
-NR₁₀-SO₂⁻, and
-NR₁₀-SO₂-NR₁₀⁻,

5 each R₅ is independently selected from the group
consisting of:

-H,
-Ar₁,
-CO-Ar₁,
10 -SO₂-Ar₁,
-R₉,
-CO-R₉,
-CO-O-R₉,
-SO₂-R₉,
15 -CO-N_{Ar₁}
 \ R₁₀,
-SO₂-N_{Ar₁}
20 \ R₁₀,
-CO-N_{R₉}
 \ R₁₀, and
25 -SO₂-N_{R₉}
 \ R₁₀,

30 R₆ and R₇, taken together form a saturated 4-8
member carbocyclic ring or heterocyclic ring
containing -O-, -S-, or -NH-, or R₇ is -H and R₆ is

-H
-Ar₁,

-R₉, or

-(CH₂)_{1,2,3}-T₁-R₉,

each R₉ is a C₁₋₆ straight or branched alkyl group
optionally singly or multiply substituted by -OH, -F,
5 or =O and optionally substituted with one or two Ar;
groups;

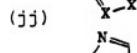
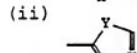
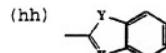
each R₁₀ is independently selected from the group
consisting of -H or a C₁₋₆ straight or branched alkyl
group;

10 each R₁₁ is independently selected from the group
consisting of -Ar₁ and -R₄,

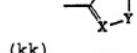
each Ar₁ is a cyclic group independently selected
from the set consisting of an aryl group which
contains 6, 10, 12, or 14 carbon atoms and between 1
15 and 3 rings, a cycloalkyl group which contains
between 3 and 15 carbon atoms and between 1 and 3
rings, said cycloalkyl group being optionally
benzofused, and a heterocycle group containing
between 5 and 15 ring atoms and between 1 and 3
rings, said heterocycle group containing at least one
20 heteroatom group selected from -O-, -S-, -SO-, -SO₂-,
=N-, and -NH-, said heterocycle group optionally
containing one or more double bonds, said heterocycle
group optionally comprising one or more aromatic
25 rings, and said cyclic group optionally being singly
or multiply substituted by =O, -OH, perfluoro C₁-
alkyl, or -Q₁;

each Ar₂ is independently selected from the
following group, in which any ring may optionally be

substituted by -Q₁:



, and



;

Ar₁ is a cyclic group selected from the set consisting of a phenyl ring, a 5-membered heteroaromatic ring, and a 6-membered heteroaromatic ring, said heteroaromatic rings comprising 1-3 heteroatom groups selected from -O-, -S-, -SO-, -SO₂-, =N-, and -NH-, said cyclic group optionally being singly or multiply substituted with =O, -OH, halogen, perfluoro C₁₋₃ alkyl, or -CO₂H;

each Q₁ is independently selected from the group consisting of

-Ar₁,
-R₉,
-T₁-R₉, and
-(CH₂)_{1,2,3}-T₁-R₉,

provided that when -Ar₁ is substituted with a Q₁ group which comprises one or more additional -Ar₁ groups, said additional -Ar₁ groups are not substituted with Q₁;

- 307 -

each X is independently selected from the group consisting of =N-, and =CH-;

each X₂ is independently selected from the group consisting of -O-, -CH₂-, -NH-, -S-, -SO-, and -SO₂-;

5 each X₃ is independently selected from the group consisting of -CH₂-, -S-, -SO-, and -SO₂-;

each X₄ is independently selected from the group consisting of -CH₂- and -NH-;

10 each X₅ is independently selected from the group consisting of -CH- and -N-;

X₆ is CH or N, provided that when X₆ is N in the R₁ group labeled (o) and X₅ is CH and X₂ is CH₂ the ring of the R₁ group labeled (o) must be substituted by Q; or benzofused;

15 each Y is independently selected from the group consisting of -O- and -S-;

each Z is independently CO or SO₂,

each a is independently 0 or 1,

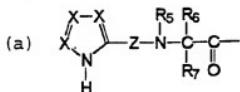
20 each c is independently 1 or 2,

each d is independently 0, 1, or 2, and

each e is independently 0, 1, 2, or 3.

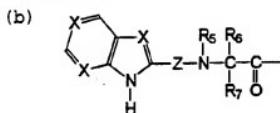
- 308 -

50. The compound according to claims 49 or
80, wherein R₁ is:



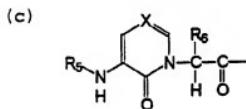
5

51. The compound according to claims 49 or
80, wherein R₁ is:



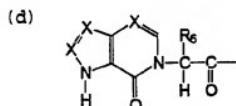
10

52. The compound according to claims 49 or
80, wherein R₁ is:



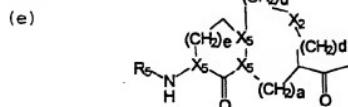
15

53. The compound according to claims 49 or
80, wherein R₁ is:



20

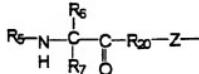
54. The compound according to claims 49 or
80, wherein R₁ is:



- 309 -

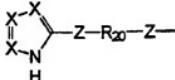
55. The compound according to claims 49 or
80, wherein R₁ is:

(f)



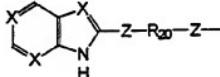
56. The compound according to claims 49 or
80, wherein R₁ is:

(g)



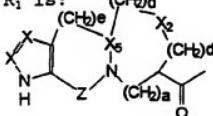
57. The compound according to claims 49 or
80, wherein R₁ is:

(h)



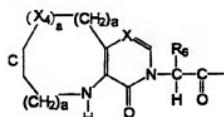
58. The compound according to claims 49 or
80, wherein R₁ is:

15 (i)



59. The compound according to claims 49 or
80, wherein R₁ is:

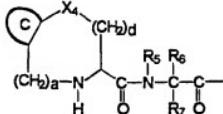
(j)



- 310 -

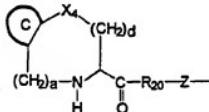
60. The compound according to claims 49 or
80, wherein R₁ is:

(k)



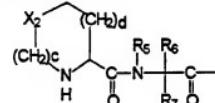
5 61. The compound according to claims 49 or
80, wherein R₁ is:

(l)



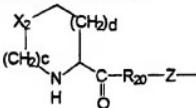
10 62. The compound according to claims 49 or
80, wherein R₁ is:

(m)



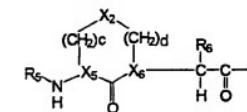
15 63. The compound according to claims 49 or
80, wherein R₁ is:

(n)



20 64. The compound according to claims 49 or
80, wherein R₁ is:

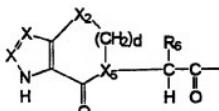
(o)



- 311 -

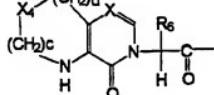
65. The compound according to claims 49 or
80, wherein R₁ is:

(p)



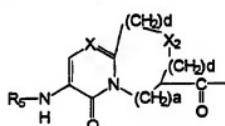
5 66. The compound according to claims 49 or
80, wherein R₁ is:

(q)



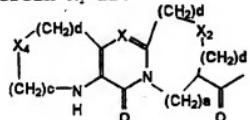
10 67. The compound according to claims 49 or
80, wherein R₁ is:

(r)



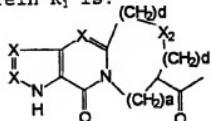
68. The compound according to claims 49 or
80, wherein R₁ is:

15 (s)



69. The compound according to claims 49 or
80, wherein R₁ is:

(t)

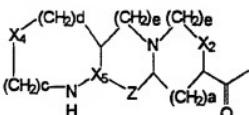


20

- 312 -

70. The compound according to claims 49 or
80, wherein R₁ is:

(v)



5

71. A pharmaceutical composition for
treating or preventing an IL-1 mediated disease
comprising a pharmaceutically effective amount of an
ICE inhibitor according to any one of claims 1-70 and
10 80-124 and a pharmaceutically acceptable carrier.

72. A pharmaceutical composition for
treating or preventing an autoimmune disease
comprising a pharmaceutically effective amount of an
ICE inhibitor according to any one of claims 1-70 and
15 80-124 and a pharmaceutically acceptable carrier.

73. A pharmaceutical composition for
treating or preventing an inflammatory disease
comprising a pharmaceutically effective amount of an
ICE inhibitor according to any one of 1-70 and 80-124
20 and a pharmaceutically acceptable carrier.

74. A pharmaceutical composition for
treating or preventing a neurodegenerative disease
comprising a pharmaceutically effective amount of an
ICE inhibitor according to any one of claims 1-70 and
25 80-124 and a pharmaceutically acceptable carrier.

- 313 -

5 75. A pharmaceutical composition for
inhibiting an ICE-mediated function comprising a
pharmaceutically effective amount of an ICE inhibitor
according to any one of claims 1-70 and 80-124 and a
pharmaceutically acceptable carrier.

10 76. A method for treating or preventing a
disease selected from the group consisting of IL-1
mediated disease, autoimmune disease, inflammatory
disease and neurodegenerative disease in a patient
comprising the step of administering to said patient
a pharmaceutical composition according to any one of
claims 71 to 75.

15 77. A method for selecting an ICE inhibitor
comprising the steps of:
20 a) selecting a candidate compound of
defined chemical structure comprising at least two
hydrogen bonding moieties, at least two moderately
hydrophobic moieties and one electronegative moiety
comprising one or more electronegative atoms attached
either to the same atom or to adjacent atoms in the
electronegative moiety;
25 b) determining a low-energy conformation
for binding of said compound to the active site of
ICE;
30 c) evaluating the capability of said
compound in said conformation to form at least two
hydrogen bonds with the non-carbon backbone atoms of
Arg-341 and Ser-339 of ICE;
 d) evaluating the capability of said
compound in said conformation to associate with at
least two of the binding pockets of ICE selected from
the group consisting of the P2 binding pocket, the P3

- 314 -

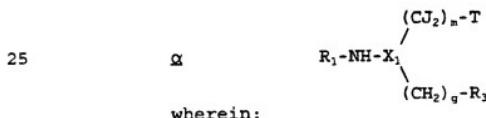
binding pocket, the P4 binding pocket and the P'
binding pocket;
e) evaluating the capability of said
compound in said conformation to interact with the P1
binding pocket of ICE; and
f) accepting or rejecting said candidate
compound as an ICE inhibitor based on the
determinations and evaluations carried out in the
preceding steps.

10 78. The method of claim 77, additionally
comprising the following steps which follow step e)
and precede step f):

g) evaluating the deformation energy of
binding of said compound to ICE; and
15 h) evaluating the contribution of the sum
of all electrostatic interactions between said
compound and ICE when said compound is bound thereto
in said conformation.

20 79. An ICE inhibitor selected by either of
the methods according to claims 77 or 78.

80. A compound represented by the formula:



X₁ is -CH;

30 g is 0 or 1;

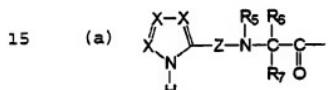
- 315 -

each J is independently selected from the group consisting of -H, -OH, and -F, provided that when a first and second J are bound to a C and said first J is -OH, said second J is -H;

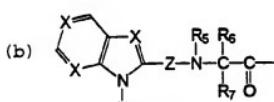
5 m is 0, 1, or 2;

T is -OH, -CO-CO₂H, -CO₂H, or any bioisosteric replacement for -CO₂H;

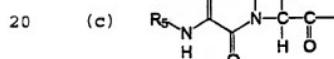
10 R₁ is selected from the group consisting of the following formulae, in which any ring may optionally be singly or multiply substituted at any carbon by Q₁, at any nitrogen by R₅, or at any atom by =O, -OH, -CO₂H, or halogen; any saturated ring may optionally be unsaturated at one or two bonds; and wherein R₁, (e) and R₁ (y) are optionally benzofused;



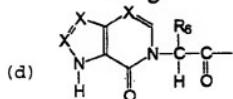
;



;



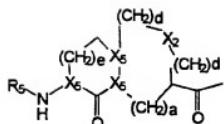
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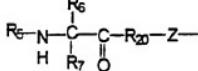
;

- 316 -

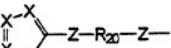
(e)



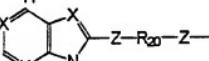
5 (f)



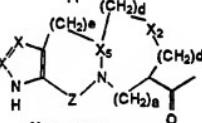
10 (g)



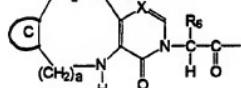
15 (h)



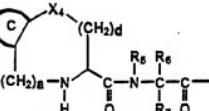
(i)



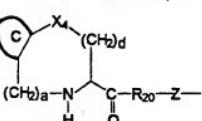
20 (j)



(k)

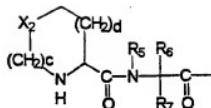


25 (l)

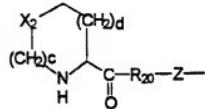


- 317 -

(m)

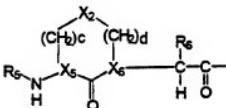


(n)



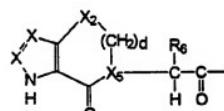
5

(o)



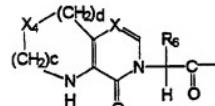
10

(p)

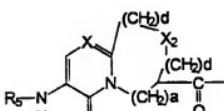


15

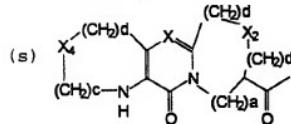
(q)



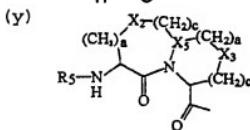
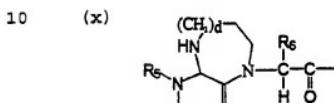
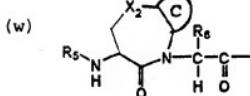
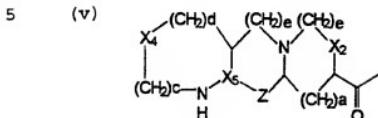
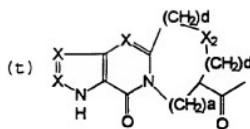
(r)



(s)



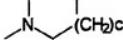
- 318 -

15 R_{20} is selected from the group consisting of:

(aa1)



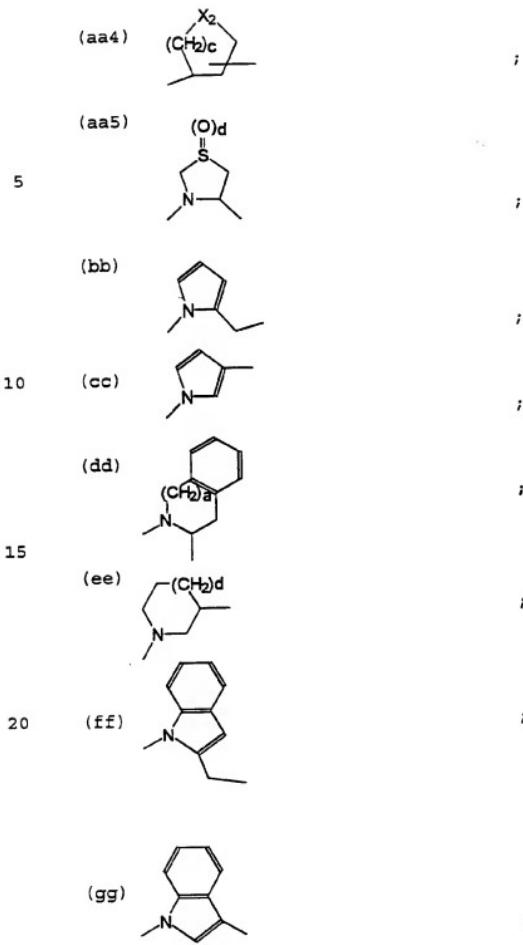
(aa2)



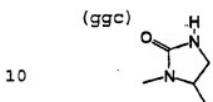
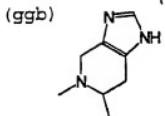
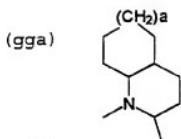
20 (aa3)



- 319 -



- 320 -



wherein each ring C is independently chosen from
the group consisting of benzo, pyrido, thieno,
pyrrolo, furano, thiazolo, isothiazolo, oxazolo,
isoxazolo, pyrimido, imidazolo, cyclopentyl, and
15 cyclohexyl;

R₃ is:

- CN,
- CH=CH-R₉,
- CH=N-O-R₉,
- 20 -(CH₂)₁₋₃-T₁-R₉,
- CJ₂-R₉,
- CO-R₁₃, or
- 25 -CO-CO-N^{/R₅}
^{\R₁₀};

each R₄ is independently selected from the group
consisting of:

- H,
- Ar₁,

- 321 -

-R₉,
-T₁-R₉, and
-(CH₂)_{1,2,3}-T₁-R₉;

each T₁ is independently selected from the group
5 consisting of:

CH=CH-,
-O-,
-S-,
-SO-,
10 -SO₂-,
-NR₁₀-,
-NR₁₀-CO-,
-CO-,
-O-CO-,
15 -CO-O-,
-CO-NR₁₀-,
-O-CO-NR₁₀-,
-NR₁₀-CO-O-,
-NR₁₀-CO-NR₁₀-,
20 -SO₂-NR₁₀-,
-NR₁₀-SO₂-, and
-NR₁₀-SO₂-NR₁₀-,

each R₅ is independently selected from the group
consisting of:

25 -H,
-Ar₁,
-CO-Ar₁,
-SO₂-Ar₁,
-CO-NH₂,
30 -SO₂-NH₂,
-R₉,
-CO-R₉,

5 -CO-O-R₉,
-SO₂-R₉,
-CO-N^{/Ar₁}
 \R₁₀,
-SO₂-N^{/Ar₁}
 \R₁₀,
10 -CO-N^{/R₉}
 \R₁₀, and
-SO₂-N^{/R₉}
 \R₁₀;

15 R₆ and R₇ taken together form a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-; or R₇ is -H and R₆ is
-H
-Ar₁,
20 -R₉,
-(CH₂)_{1,2,3}-T₁-R₉, or
an α-amino acid side chain residue;

25 each R₉ is a C₁₋₆ straight or branched alkyl group optionally singly or multiply substituted by -OH, -F, or =O and optionally substituted with one or two Ar₁ groups;

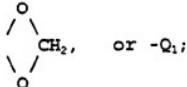
each R₁₀ is independently selected from the group consisting of -H or a C₁₋₆ straight or branched alkyl group;

30 each R₁₃ is independently selected from the group

- 323 -

consisting of -Ar₂, -R₄ and -N-OH
 |
 R₅;

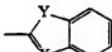
each Ar₁ is a cyclic group independently selected
 5 from the set consisting of an aryl group which
 contains 6, 10, 12, or 14 carbon atoms and between 1
 and 3 rings, a cycloalkyl group which contains
 between 3 and 15 carbon atoms and between 1 and 3
 rings, said cycloalkyl group being optionally
 10 benzofused, and a heterocycle group containing
 between 5 and 15 ring atoms and between 1 and 3
 rings, said heterocycle group containing at least one
 heteroatom group selected from -O-, -S-, -SO-, -SO₂-,
 -N-, and -NH-, said heterocycle group optionally
 15 containing one or more double bonds, said heterocycle
 group optionally comprising one or more aromatic
 rings, and said cyclic group optionally being singly
 or multiply substituted by -NH₂, -CO₂H, -Cl, -F, -Br,
 -I, -NO₂, -CN,
 20 =O, -OH, -perfluoro C₁₋₃ alkyl,



25 or -Q₁;

each Ar₂ is independently selected from the
 following group, in which any ring may optionally be
 singly or multiply substituted by -Q₁ and -Q₂:

(hh)



;

(ii)

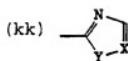


;

(jj)



; and



;

each Q_1 is independently selected from the group
5 consisting of:

- Ar₁,
- O-Ar₁,
- R₉,
- T₁-R₉, and
- 10 -(CH₂)_{1,2,3}-T₁-R₉;

each Q_2 is independently selected from the group
consisting of -OH, -NH₂, -CO₂H, -Cl, -F, -Br, -I,
15 -NO₂, -CN, -CF₃, and



provided that when -Ar₁ is substituted with a Q_1
20 group which comprises one or more additional -Ar₁
groups, said additional -Ar₁ groups are not
substituted with Q_1 ;

each X is independently selected from the group
consisting of =N-, and =CH-;

25 each X₂ is independently selected from the group
consisting of -O-, -CH₂-, -NH-, -S-, -SO-, and -SO₂-;

each X₃ is independently selected from the group
consisting of -CH₂-, -S-, -SO-, and -SO₂-;

30 each X₄ is independently selected from the group
consisting of -CH₂- and -NH-;

- 325 -

each X₅ is independently selected from the group
consisting of -CH- and -N-;
| |

X₆ is -CH- or -N-;

5 each Y is independently selected from the group
consisting of -O-, -S-, and -NH;

each Z is independently CO or SO₂;

each a is independently 0 or 1;

each c is independently 1 or 2;

10 each d is independently 0, 1, or 2; and

each e is independently 0, 1, 2, or 3;

provided that when

R₁ is (f),

15 R₆ is an α-amino acid side chain residue, and

R₇ is -H,

then (aa1) and (aa2) must be substituted with Q₁;

also provided that when

20 R₁ is (o),
g is 0,
J is -H,
m is 1,
R₆ is an α-amino acid side chain residue,
25 R₇ is -H,
X₂ is -CH₂-,
X₅ is -CH- ,
|

- 326 -

X₆ is -N- , and

|

R₃ is /R₁₀
-CO-N
\\R₁₀ , or -CO-R₁₃, when

5

R₁₃ is:

-CH₂-O-CO-Ar₁,
-CH₂-S-CO-Ar₁,
-CH₂-O-Ar₁,
-CH₂-S-Ar₁, or
-R₄ when -R₄ is -H;

10

then the ring of the R₁(o) group must be substituted with Q₁ or benzofused; and

15

provided that when

R₁ is (w),

g is 0,

J is -H,

m is 1,

20

T is -CO₂H,

X₂ is O,

R₅ is benzyloxycarbonyl, and

ring C is benzo,

then R₃ cannot be -CO-R₁₃, when:

25

R₁₃ is -CH₂-O-Ar₁ and

Ar₁ is 1-phenyl-3-trifluoromethyl-pyrazole-5-yl wherein the phenyl is optionally substituted with a chlorine atom;

or when

30

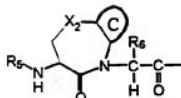
R₁₃ is -CH₂-O-CO-Ar₁, wherein

Ar₁ is 2,6-dichlorophenyl.

- 327 -

81. The compound according to claim 80,
wherein R₁ is:

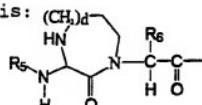
(w)



5

82. The compound according to claim 80,
wherein R₁ is: (CH₂)_d

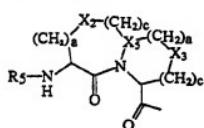
(x)



10

83. The compound according to claim 80,
wherein R₁ is:

(y)



15

84. The compound according to claim 80,
wherein:

X₁ is -CH;

g is 0;

20

J is -H;

m is 0 or 1 and T is -CO-CO₂H, or any bioisosteric
replacement for -CO₂H, or

m is 1 and T is -CO₂H;

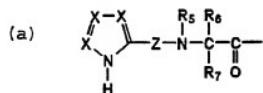
25

R₁ is selected from the group consisting of the
following formulae, in which any ring may optionally
be singly or multiply substituted at any carbon by

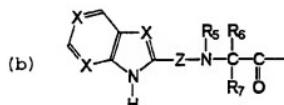
- 328 -

Q_1 , at any nitrogen by R_5 , or at any atom by =O, -OH, -CO₂H, or halogen, and wherein (e) is optionally benzofused:

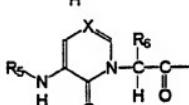
5



10

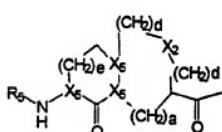


(c)

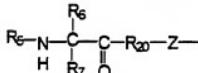


15

(e)

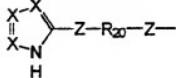


(f)

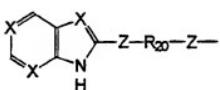


15

(g)

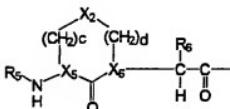


(h)

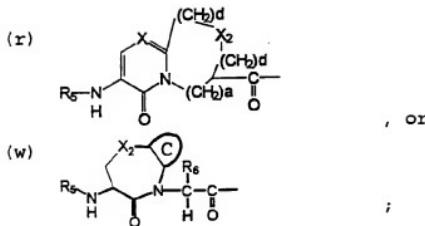


20

(o)



- 329 -



5

 R_{20} is:

(aa1)

, or

(aa2)

10

and c is 1;

ring C is benzo optionally substituted with
 $-C_{1-3}$ alkyl, $-O-C_{1-3}$ alkyl, $-Cl$, $-F$ or $-CF_3$;

15

when R_1 is (a) or (b), R_5 is preferably $-H$, andwhen R_1 is (c), (e), (f), (o), (r), (w), (x) or
(y), R_5 is preferably:

20

- $-CO-Ar_1$
- $-SO_2-Ar_1$,
- $-CO-NH_2$,
- $-CO-NH-Ar_1$
- $-CO-R_9$,
- $-CO-O-R_9$,

- 330 -

-SO₂-R₉, or

-CO-NH-R₉,

R₇ is -H and R₆ is: -H,
5 -R₉, or
-Ar₁;

R₉ is a C₁₋₆ straight or branched alkyl group
optionally substituted with =O and optionally
substituted with -Ar₁;

10 R₁₀ is -H or a -C₁₋₃ straight or branched alkyl
group;

15 Ar₁ is phenyl, naphthyl, pyridyl, benzothiazolyl,
thienyl, benzothienyl, benzoxazolyl, 2-indanyl, or
indolyl substituted with -O-C₁₋₃ alkyl, -NH-C₁₋₃ alkyl,
-N-(C₁₋₃ alkyl)₂, -Cl, -F, -CF₃,
-C₁₋₃ alkyl, or O
 / \ ;
 \ /
 O

20 Q₁ is R₉ or -(CH₂)_{0,1,2}-T₁-(CH₂)_{0,1,2}-Ar₁, wherein
T₁ is -O- or -S-;

each X is independently selected from the group
consisting of =N-, and =CH-;

25 each X₂ is independently selected from the group
consisting of -O-, -CH₂-, -NH-, -S-, -SO-, and -SO₂-;

each X₅ is independently selected from the group
consisting of -CH- and -N-;
| |

- 331 -

X₆ is -CH- or -N-,
 | |

provided that when:

R₁ is R₁(o),

5 X₂ is -CH₂-,

X₅ is -CH- , and
 |

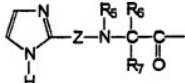
10 X₆ is -N- ,
 |

then the ring of the R₁(o) group must be
 substituted with Q₁ or benzofused; and

Z is C=O.

15 85. The compound according to claim 84,
 wherein the R₁ group is

(a2)



optionally substituted with Q₁, wherein

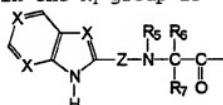
R₆ is -H;

20 R₇ is -H; and

Z is C=O.

86. The compound according to claim 84,
 wherein the R₁ group is

(b)



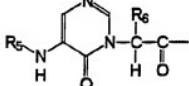
optionally substituted with Q₁, wherein

- 332 -

R₅ is -H;
R₇ is -H; and
Z is C=O.

87. The compound according to claim 84,
5 wherein the R₁ group is

(c1)



which is optionally substituted with Q₁;

10

provided that when R₁ is (c1),

g is 0,

J is -H,

m is 1,

15

T is -CO₂H,

X is N,

R₅ is benzyloxycarbonyl, and

R₆ is -H,

then R₃ cannot be -CO-R₁₃ when

20

R₁₃ is -CH₂-O-Ar₁ and

Ar₁ is 1-phenyl-3-trifluoromethyl-pyrazole-5-yl, wherein the phenyl is optionally substituted with a chlorine atom; or when

25

R₁₃ is -CH₂-O-CO-Ar₁, wherein

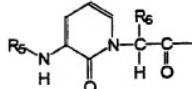
Ar₁ is 2,6-dichlorophenyl,

and when the 2-position of the scaffold ring is substituted with para-fluoro-phenyl.

- 333 -

88. The compound according to claim 84,
wherein the R₁ group is:

(c2)

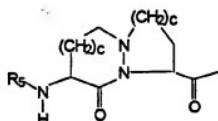


5

which is optionally substituted with Q₁.

89. The compound according to claim 84,
wherein the R₁ group is:

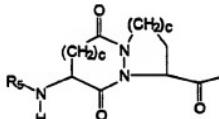
(e1)



10

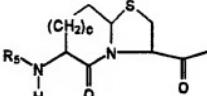
, or

(e2)



and c is 2; or

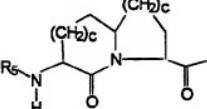
(e4)



15

, or

(e7)



which is optionally benzofused,
and c is 1 or 2;

provided that when R₁ is (e4),

- 334 -

g is 0,
J is -H,
m is 1,
T is -CO₂H,
5 R₅ is benzyloxycarbonyl, and
c is 1,

then R₃ cannot be -CO-R₁₃ when
R₁₃ is -CH₂-O-Ar₁ and
Ar₁ is 1-phenyl-3-trifluoromethyl-pyrazole-
10 5-yl, wherein the phenyl is optionally substituted
with a chlorine atom; or when

R₁₃ is -CH₂-O-CO-Ar₁, wherein
Ar₁ is 2,6-dichlorophenyl,
15 and when the 2-position of the scaffold ring is
substituted with para-fluoro-phenyl; and

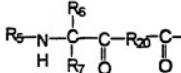
also provided that when
R₁ is (e7),
g is 0,
20 J is -H,
m is 1,
T is -CO₂H or -CO-NH-OH,
R₅ is a protective group for the N atom of an
amino acid side chain residue, and
25 each c is 1,

then R₃ cannot be -CO-R₁₃ when
R₁₃ is:
-CH₂-O-CO-Ar₁,
-CH₂-S-CO-Ar₁,
30 -CH₂-O-Ar₁, or
-CH₂-S-Ar₁.

- 335 -

90. The compound according to claim 84,
wherein the R₁ group is

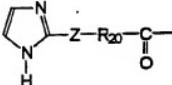
(f1)



5 91. The compound according to claim 84,

wherein the R₁ group is

(g2)



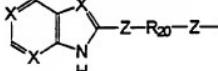
, wherein

10 R₂₀ is (aa1) optionally substituted singly or
multiply with Q₁; and

Z is C=O.

92. The compound according to claim 84,
wherein the R₁ group is

(h)



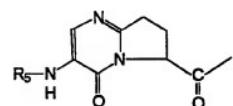
, wherein

15 R₂₀ is (aa1) optionally substituted singly or
multiply with Q₁; and

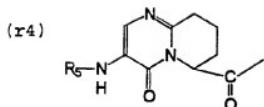
Z is C=O.

93. The compound according to claim 84,
20 wherein the R₁ group is:

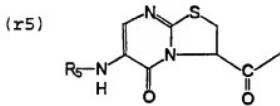
(r3)



- 336 -



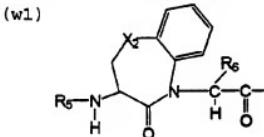
;



; and

optionally substituted with Q₁.

5 94. The compound according to claim 84,
wherein the R₁ group is



; wherein

X₂ is:

- 10 -O-,
 -S-,
 -SO₂-, or
 -NH-;

15 optionally substituted with R₅ or Q₁ at X₂ when X₂
is -NH-; and

ring C is benzo substituted with -C₁₋₃ alkyl,
-O-C₁₋₃ alkyl, -Cl, -F or -CF₃.

20 95. The compound according to claim 84,
wherein

R₃ is:

- 337 -

-CO-R₁₃, or
 -CO-CO-N-R₉,
 \
 R₁₀;

5 T₁ is:

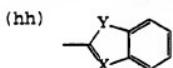
-O- or
 -S-;

R₉ is a C₁₋₆ straight or branched alkyl group
 optionally substituted with =O and optionally
 10 substituted with Ar₁; and

15 R₁₃ is:

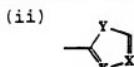
-H,
 -R₉,
 -Ar₂, or
 -CH₂-T₁-R₉.

96. The compound according to claim 95,
 wherein -Ar₂ is:



20 optionally substituted singly or multiply with
 -C₁₋₆ alkyl, -O-C₁₋₆ alkyl, -NH-C₁₋₆ alkyl, -N-(C₁₋₆
 alkyl)₂, -S-C₁₋₆ alkyl, -Cl, -F, -CF₃, or
 25

97. The compound according to claim 95,
 wherein -Ar₂ is:



- 338 -

(jj)



, or

(kk)



5

98. The compound according to claim 95,
wherein:

R₁₃ is -CH₂-O-R₉; wherein:

10 R₉ is a C₁₋₆ straight or branched alkyl group
optionally substituted with =O and optionally
substituted with Ar₁.

99. The compound according to claim 95,
wherein:

R₁₃ is -CH₂-S-R₉; wherein:

15 R₉ is a C₁₋₆ straight or branched alkyl group
optionally substituted with Ar₁.

100. The compound according to claim 98,
wherein:

R₁₃ is -CH₂-O-R₉; wherein:

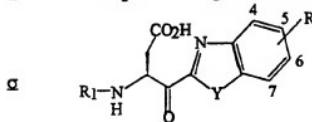
20 R₉ is a C₁₋₆ straight or branched alkyl group
optionally substituted with Ar₁.

101. The compound according to claim 95,
wherein:

R₁₃ is H.

- 339 -

102. A compound represented by the formula:



wherein the ring is optionally substituted with
one or more R groups, preferably 0, 1 or 2; and
5 wherein:

R₁ is R₅-(A)_p-;

R₅ is selected from the group consisting of:

-H,

-Ar₁,

10 -CO-Ar₁,

-SO₂-Ar₁,

-R₉,

-CO-R₉,

-CO-O-R₉,

15 -SO₂-R₉,

/Ar₁

-CO-N
 \|R₁₀,

20 -SO₂-N
 /Ar₁
 \|R₁₀,

25 -CO-N
 /R₉
 \|R₁₀, and

-SO₂-N
 /R₉
 \|R₁₀;

30 each A is independently selected from the group
consisting of any α-amino acid;

- 340 -

p is 0, 1, 2, 3 or 4;

Y is

-O-,
-S- or
-NH; and

5

R is:

-H,
-O-C₁₋₆ alkyl,
-NH(C₁₋₆ alkyl),
10 -N(C₁₋₆ alkyl)₂,
-S-C₁₋₆ alkyl,
-C₁₋₆ alkyl, or
-Q₂;

each R, is a C₁₋₆ straight or branched alkyl group
15 optionally singly or multiply substituted by -OH, -F,
or =O and optionally substituted with one Ar₁ group;

each R₁₀ is independently selected from the group
consisting of -H or a C₁₋₆ straight or branched alkyl
group;

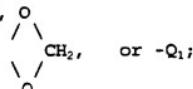
20 each T, is independently selected from the group
consisting of:

-CH=CH-,
-O-,
-S-,
25 -SO-,
-SO₂-,
-NR₁₀-,
-NR₁₀-CO-,
-CO-,
30 -O-CO-,

- 341 -

-CO-O-,
-CO-NR₁₀-,
-O-CO-NR₁₀-,
-NR₁₀-CO-O-,
5 -NR₁₀-CO-NR₁₀-,
-SO₂-NR₁₀-,
-NR₁₀-SO₂- , and
-NR₁₀-SO₂-NR₁₀- ,

each Ar₁ is a cyclic group independently selected
10 from the set consisting of an aryl group which
contains 6, 10, 12, or 14 carbon atoms and between 1
and 3 rings, a cycloalkyl group which contains
between 3 and 15 carbon atoms and between 1 and 3
rings, said cycloalkyl group being optionally
15 benzofused, and a heterocycle group containing
between 5 and 15 ring atoms and between 1 and 3
rings, said heterocycle group containing at least one
heteroatom group selected from -O-, -S-, -SO-, -SO₂-,
=N-, and -NH-, said heterocycle group optionally
20 containing one or more double bonds, said heterocycle
group optionally comprising one or more aromatic
rings, and said cyclic group optionally being singly
or multiply substituted by -NH₂, -CO₂H, -Cl, -F, -Br,
-I, -NO₂, -CN, =O, -OH,
25 -perfluoro C₁₋₁₀ alkyl, O



30 each Q₁ is independently selected from the group
consisting of:

-Ar₁,
-R₉,
-T₁-R₉, and

- 342 -

- (CH₂)_{1,2,3}-T₁-R₉;

each Q₂ is independently selected from the group consisting of -OH, -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂, -CN, -CF₃, and

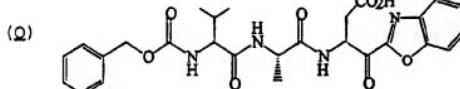
5



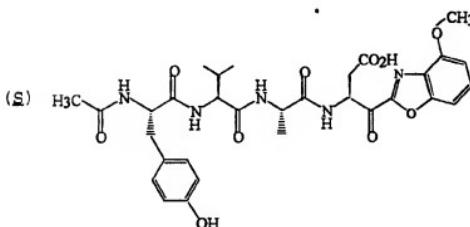
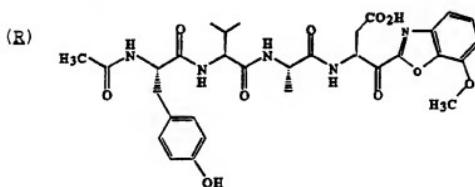
provided that when -Ar₁ is substituted with a Q₁ group which comprises one or more additional -Ar₁ groups, said additional -Ar₁ groups are not substituted with Q₁.

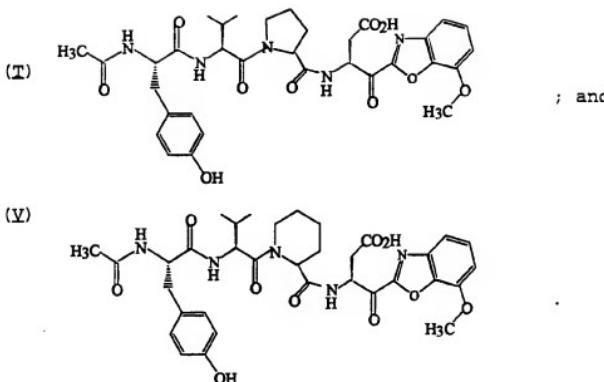
103. A compound according to claim 102 selected from the group consisting of:

15



20





5

104. A compound according to claim 102
wherein each A is independently selected from the
group consisting of the α -amino acids:

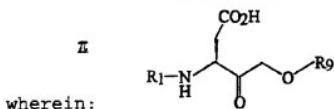
- alanine,
- histidine,
- lysine,
- phenylalanine,
- proline,
- tyrosine,
- valine,
- leucine,
- isoleucine,
- glutamine,
- methionine,
- homoproline,
- 3-(2-thienyl) alanine, and
- 3-(3-thienyl) alanine.

15

20

- 344 -

105. A compound represented by the formula:

5 R_1 is $\text{R}_5\text{-}(\text{A})_{\text{p}}\text{-}$;

each T_1 is independently selected from the group consisting of:

- CH=CH-,
- O-,
- 10 -S-,
- SO-,
- SO₂-,
- NR₁₀⁻,
- NR₁₀⁻CO-,
- 15 -CO-,
- O-CO-,
- CO-O-,
- CO-NR₁₀⁻,
- O-CO-NR₁₀⁻,
- 20 -NR₁₀⁻CO-O-,
- NR₁₀⁻CO-NR₁₀⁻,
- SO₂-NR₁₀⁻,
- NR₁₀⁻SO₂-, and
- NR₁₀⁻SO₂-NR₁₀⁻;

25

R_5 is selected from the group consisting of:

- H,
- Ar₁,
- CO-Ar₁,
- 30 -SO₂-Ar₁,
- R₉,

- 345 -

-CO-R₉,
-CO-O-R₉,
-SO₂-R₉,
5 /Ar₁
-CO-N \R₁₀,
 /Ar₁
-SO₂-N \R₁₀,
10 /R₉
-CO-N \R₁₀, and
 /R₉
-SO₂-N \R₁₀;
15

each A is independently selected from the group consisting of any α -amino acid;

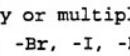
p is 0, 1, 2, 3 or 4;

each R₉ is a C₁₋₆ straight or branched alkyl group optionally singly or multiply substituted by -OH, -F, or =O and optionally substituted with an Ar₁ group;

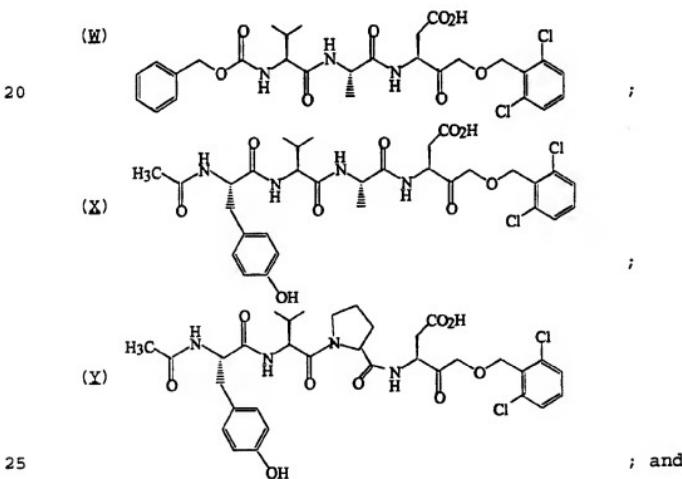
each R₁₀ is independently selected from the group consisting of -H or a C₁₋₆ straight or branched alkyl group;

25 Ar₁ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 15 carbon atoms and between 1 and 3 rings, said cycloalkyl group being optionally benzofused, and a
30

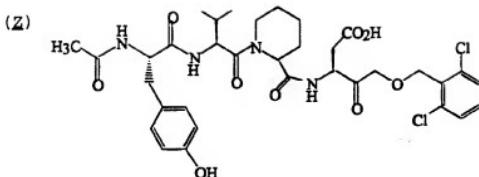
- 346 -

heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocycle group containing at least one heteroatom group selected from -O-, -S-, -SO-, -SO₂-, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂, -CH₃, =O, -OH, -perfluoro C₁₋₃ alkyl, 

106. A compound according to claim 105 selected from the group consisting of:

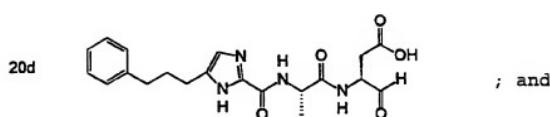


- 347 -

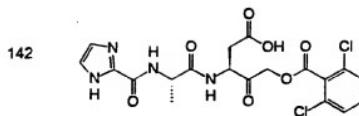


107. A compound according to claim 105
wherein each A is independently selected from the
5 group consisting of the α -amino acids:
 alanine,
 histidine,
 lysine,
 phenylalanine,
 10 proline,
 tyrosine,
 valine,
 leucine,
 isoleucine,
 15 glutamine,
 methionine,
 homoproline,
 3-(2-thienyl) alanine, and
 3-(3-thienyl) alanine.

- 20 108. The compound according to claim 85,
selected from the group consisting of:

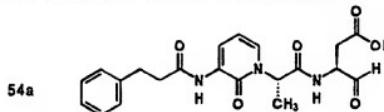


- 348 -

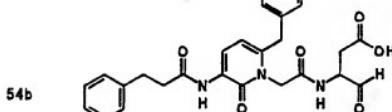


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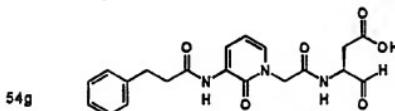
109. The compound according to claim 88,
selected from the group consisting of



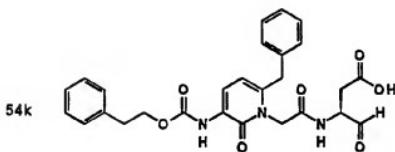
10



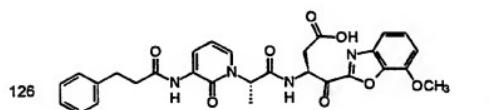
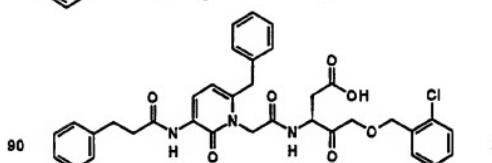
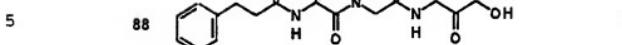
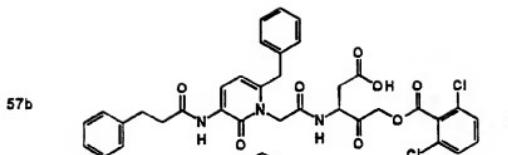
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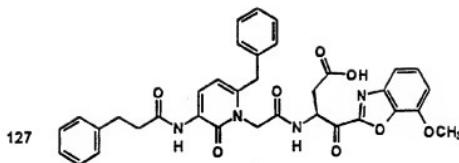


- 349 -

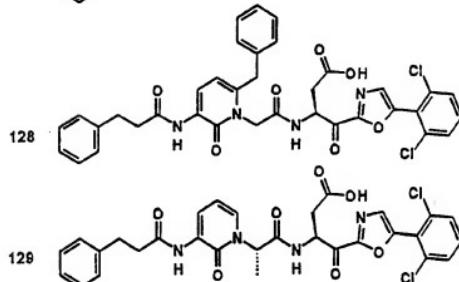


- 350 -

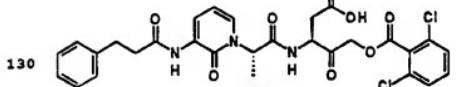
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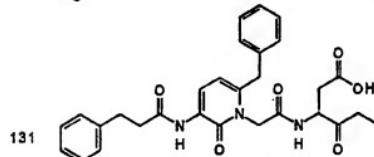


15



; and

20

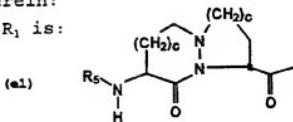


- 351 -

110. The compound according to claim 89,

wherein:

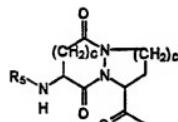
R₁ is:



5

, or

(e2)



and c is 2;

10

m is 1;

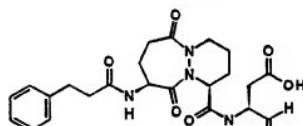
T is -CO₂H; and

R₃ is -CO-R₁₃.

15

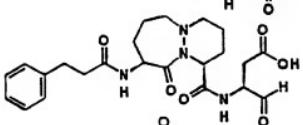
111. The compound according to claim 110,
selected from the group consisting of:

47a

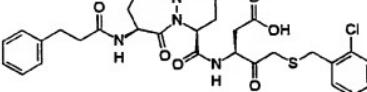


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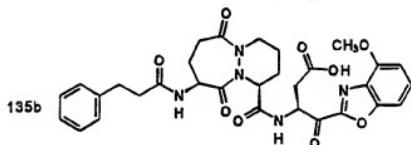
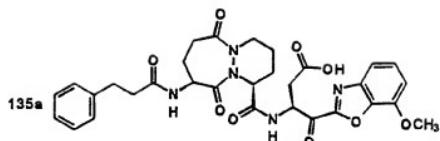
47b



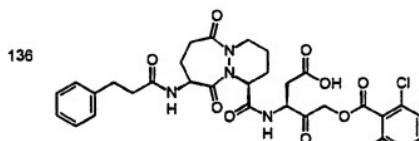
125b



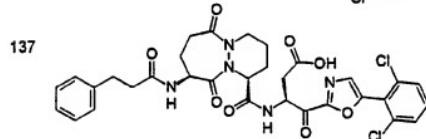
- 352 -



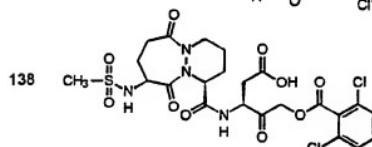
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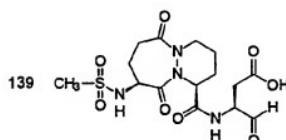
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15



; and

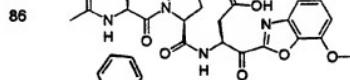


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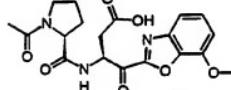
- 353 -

112. The compound according to claim 90,
selected from the group consisting of:

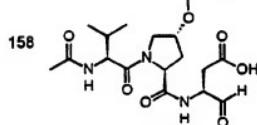
5



87

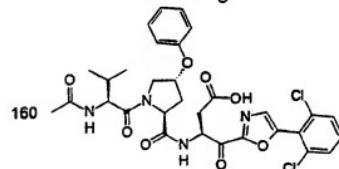


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; and

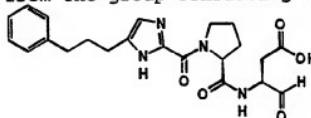
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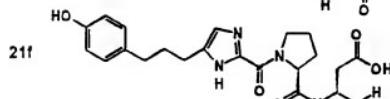
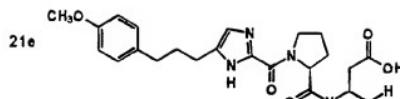
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113. The compound according to claim 91,
selected from the group consisting of:

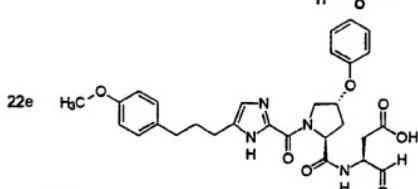
21d



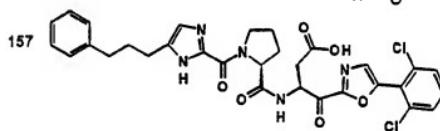
- 354 -



5



; and



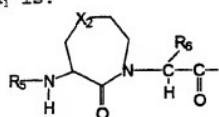
10

114. The compound according to claim 84,
wherein:

15

 R_1 is:

(o6)

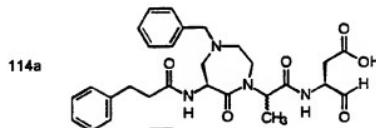


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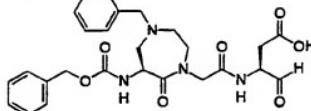
 X_2 is $-NH-$; m is 1; T is $-CO_2H$; R_3 is $-CO-R_{13}$.

- 355 -

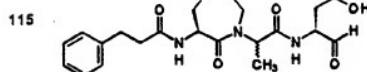
115. The compound according to claim 114,
selected from the group consisting of:



5
114b

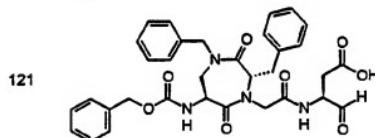


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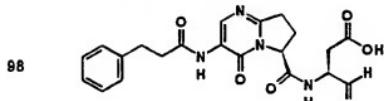


; and

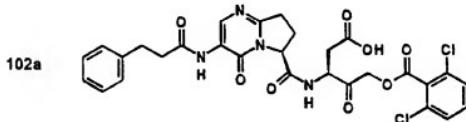
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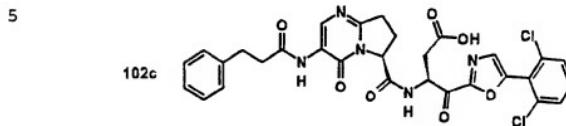
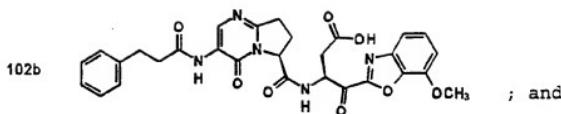
116. The compound according to claim 93,
selected from the group consisting of:



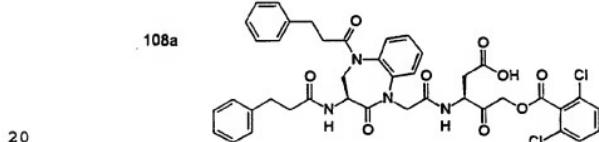
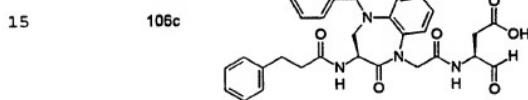
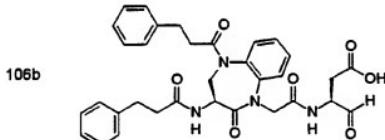
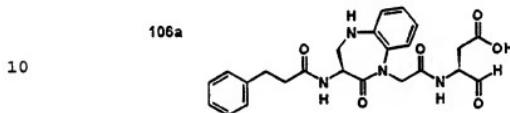
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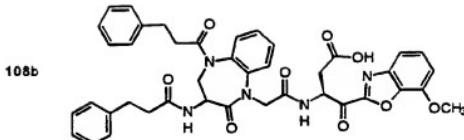
- 356 -



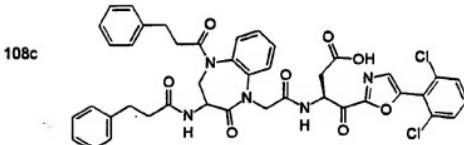
117. The compound according to claim 94,
selected from the group consisting of:



- 357 -



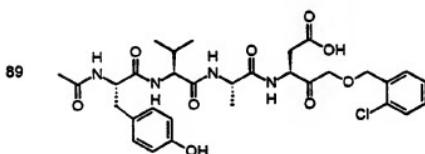
; and



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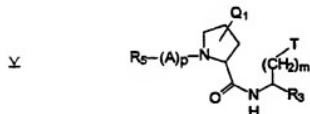
118. The compound according to claim 105:

10



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119. A compound represented by the formula:



wherein:

m is 0, 1, or 2

20 T is $-\text{CO}_2\text{H}$, or any bioisosteric replacement for
 $-\text{CO}_2\text{H}$

- 358 -

R₃ is

-CN,

-CO-R₁₃, or

5 /R₅
-CO-CO-N
 \R₁₀;

R₅ is selected from the group consisting of:

-H,

-Ar₁,

10 -CO-Ar₁,

-SO₂-Ar₁,

-R₉,

-CO-R₉,

-CO-O-R₉,

15 -SO₂-R₉,

 /Ar₁
-CO-N
 \R₁₀,

20 -SO₂-N
 /Ar₁
 \R₁₀,

 /R₉
-CO-N
 \R₁₀, and

25 -SO₂-N
 /R₉
 \R₁₀;

each A is independently selected from the group
30 consisting of any α -amino acid;

p is 2 or 3;

each R₉ is a C₁₋₆ straight or branched alkyl group
optionally singly or multiply substituted by -OH, -F,

or =O and optionally substituted with one Ar₁ group;

each T₁ is independently selected from the group consisting of:

- CH=CH-,
- 5 -O-,
- S-,
- SO-,
- SO₂-,
- NR₁₀-,
- 10 -NR₁₀-CO-,
- CO-,
- O-CO-,
- CO-O-,
- CO-NR₁₀-,
- 15 -O-CO-NR₁₀-,
- NR₁₀-CO-O-,
- NR₁₀-CO-NR₁₀-,
- SO₂-NR₁₀-,
- NR₁₀-SO₂-, and
- 20 -NR₁₀-SO₂-NR₁₀-,

each R₁₀ is independently selected from the group consisting of -H or a -C₁₋₆ straight or branched alkyl group;

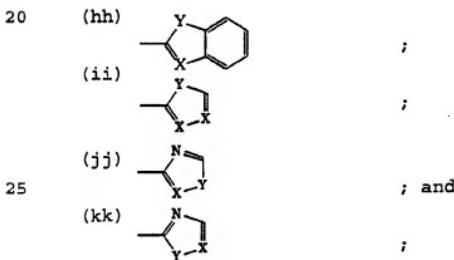
each R₁₃ is independently selected from the group consisting of H, R₉, Ar₂, and -CH₂-T₁-R₉,

each Ar₁ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 15 carbon atoms and between 1 and 3

- 360 -

rings, said cycloalkyl group being optionally benzofused, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocycle group containing at least one 5 heteroatom group selected from $-O-$, $-S-$, $-SO-$, $-SO_2-$, $=N-$, and $-NH-$, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic 10 rings, and said cyclic group optionally being singly or multiply substituted by $-NH_2$, $-CO_2H$, $-Cl$, $-F$, $-Br$, $-I$, $-NO_2$, $-CN$, $=O$, $-OH$, 15 $-perfluoro C_1$, alkyl, $\begin{array}{c} O \\ / \backslash \\ CH_2, \text{ or } -Q_1; \text{ and} \\ \backslash / \\ O \end{array}$

each Ar_2 is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by $-Q_1$ and $-Q_2$:



each Q_1 is independently selected from the group consisting of:

- 30 $-Ar_1$
 $-O-Ar_1$
 $-R_9$,

- 361 -

-T₁-R₉, and

- (CH₂)_{1,2,3}-T₁-R₉;

each Q₂ is independently selected from the group
5 consisting of -OH, -NH₂, -CO₂H, -Cl, -F, -Br, -I,
-NO₂, -CN, -CF₃, and

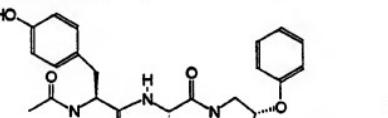


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provided that when -Ar₁ is substituted with a Q₁ group which comprises one or more additional -Ar₁ groups, said additional -Ar₁ groups are not
15 substituted with Q₁.

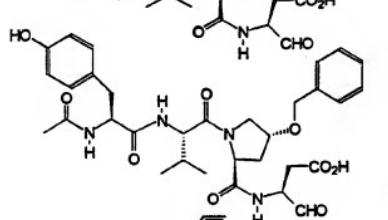
120. The compound according to claim 119,
selected from the group consisting of:

I

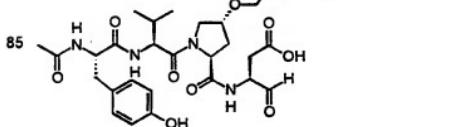


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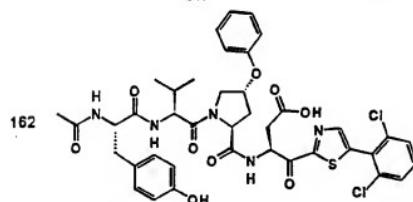
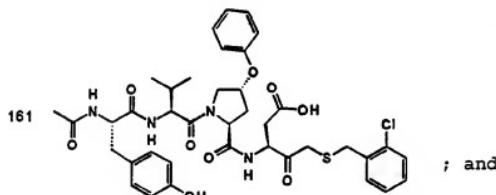
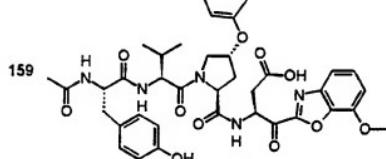
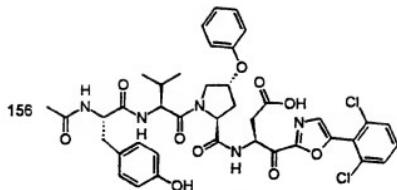
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- 362 -



121. The compound according to claim 119,
wherein each A is independently selected from the
group consisting of the α -amino acids:

- 15 alanine,
 histidine,

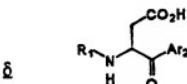
5

lysine,
phenylalanine,
proline,
tyrosine,
valine,
leucine,
isoleucine,
glutamine,
methionine,
homoproline,
10
3-(2-thienyl) alanine, and
3-(3-thienyl) alanine.

10

122. A compound represented by the formula:

15



R_1 is $\text{R}_5-(\text{A})_p-$;

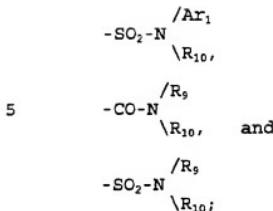
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R_5 is selected from the group consisting of:

25

- H,
- Ar₁,
- CO-Ar₁,
- SO₂-Ar₁,
- R₉,
- CO-R₉,
- CO-O-R₉,
- SO₂-R₉,
- /Ar₁
- CO-N
- \R₁₀,

- 364 -



10 each A is independently selected from the group consisting of any α -amino acid;

p is 0, 1, 2, 3 or 4;

15 each R₉ is a C₁₋₆ straight or branched alkyl group optionally singly or multiply substituted by -OH, -F, or =O and optionally substituted with one Ar₁ group;

each R₁₀ is independently selected from the group consisting of -H or a C₁₋₆ straight or branched alkyl group;

20 each T₁ is independently selected from the group consisting of:

-CH=CH-,
-O-,
-S-,
-SO-,

25 each Ar₁ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 15 carbon atoms and between 1 and 3

- 365 -

rings, said cycloalkyl group being optionally benzofused, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocycle group containing at least one heteroatom group selected from -O-, -S-, -SO-, -SO₂-, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -NH₂, -CO₂H,
 5 -Cl, -F, -Br, -I, -NO₂, -CN, =O, -OH,
 10 -perfluoro C₁₋₃ alkyl,

O
 / \ CH₂, or -Q₁; and
 15 \ / O

each Ar₂ is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by -Q₁ and -Q₂:

20 (ii)



;

(jj)



; and

25 (kk)



;

each Q₁ is independently selected from the group consisting of:

30

-Ar₁

-O-Ar₁

-R₉,

-T₁-R₉,

and

- 366 -

- (CH₂)_{1,2,3}-T₁-R₉;

each Q₂ is independently selected from the group consisting of -OH, -NH₂, -CO₂H, -Cl, -F, -Br, -I,

5 -NO₂, -CN, -CF₃, and



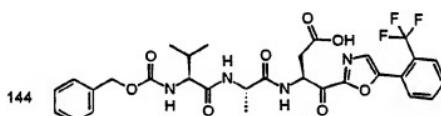
10 provided that when -Ar₁ is substituted with a Q₁ group which comprises one or more additional -Ar₁ groups, said additional -Ar₁ groups are not substituted with Q₁;

15 each X is independently selected from the group consisting of =N-, and =CH-; and

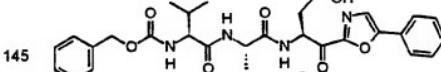
each Y is independently selected from the group consisting of -O-, -S-, and -NH.

123. The compound according to claim 122, selected from the group consisting of:

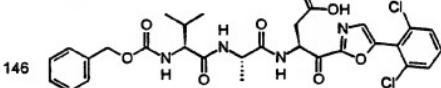
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;

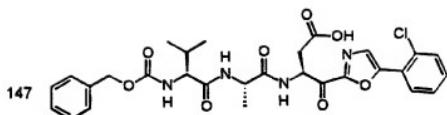


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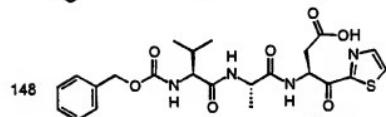


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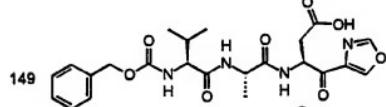
- 367 -



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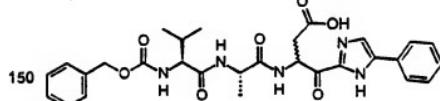


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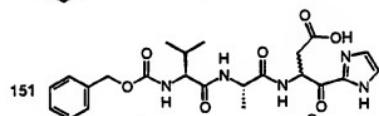


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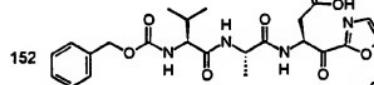


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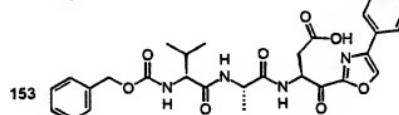
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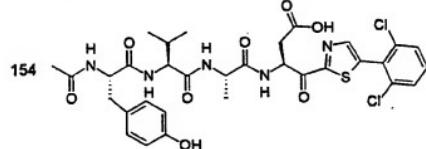


i

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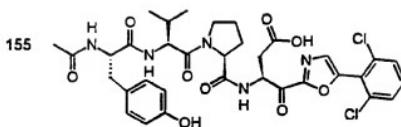


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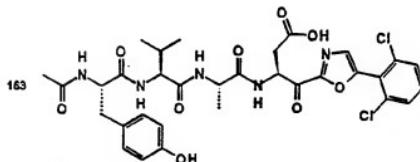


i

- 368 -



; and



124. The compound according to claim 122,

5 wherein each A is independently selected from the
group consisting of the α -amino acids:

- 10 alanine,
histidine,
lysine,
phenylalanine,
proline,
tyrosine,
valine,
leucine,
15 isoleucine,
glutamine,
methionine,
homoproline,
3-(2-thienyl) alanine, and
20 3-(3-thienyl) alanine.

INTERNATIONAL SEARCH REPORT

Internat'l Application No

PCT/US 95/07617

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 C07K5/023 A61K38/06 A61K38/07

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>NATURE (LONDON) (1994), 370(6487), 270-5 CODEN: NATUAS;ISSN: 0028-0836, 28 July 1994 WILSON, KEITH P. ET AL 'Structure and mechanism of interleukin -1.beta. converting enzyme' see page 270, right column, paragraph 2 see page 273, right column, last paragraph - page 274, right column, last paragraph; figures 4,5; table 1 ---- -/-</p>	1-18,49, 55, 71-80, 84,90

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which may be cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 October 1995	16.11.95
Name and mailing address of the ISA European Patent Office, P.O. 5818 Patenttaan 2 NL-2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Authorized officer Fuhr, C

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/US 95/07617

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BIOCHEMISTRY, vol. 33, no. 13, 5 April 1994 EASTON, PA US, pages 3934-3940, N.A. THORNBERRY ET AL. 'Inactivation of Interleukin-1beta Converting Enzyme by Peptide (Acyloxy)methyl Ketones' see page 3938, right column, last paragraph - page 3940, left column, paragraph 3; tables 1,2 ---	1-18, 49, 55, 71-80, 84, 90, 105, 107
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 37, no. 5, 4 March 1994 WASHINGTON US, pages 563-564, R.E. DOLL ET AL. 'P1 Aspartate-Based Peptide alpha-((2,6-Dichlorobenzoyl)oxy)methyl Ketones as Potent Time-Dependent Inhibitors of Interleukin-1beta-Converting Enzyme' see scheme 1 see table 1 ---	1-18, 49, 55, 71-80, 84, 90, 105, 107
X	EP,A,0 519 748 (MERCK & CO INC) 23 December 1992 see claims; examples ---	1-18, 49, 55, 71-80, 84, 90, 105, 107
X	WO,A,93 09135 (SANDOZ AG ;SANDOZ AG (DE); SANDOZ LTD (CH)) 13 May 1993 see claims; examples ---	1-18, 23, 26, 47-49, 71-80, 84, 105, 107, 119
X	WO,A,93 14777 (MERCK & CO INC) 5 August 1993 see claims; examples ---	1-18, 49, 55, 71-80, 84, 90, 105, 107
X	WO,A,93 16710 (MERCK & CO INC) 2 September 1993 see claims; examples ---	1-18, 49, 55, 71-80, 84, 90, 105, 107
3		-/-

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/US 95/07617

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 529 713 (MERCK & CO INC) 3 March 1993 see claims; examples ____	1-18,49, 55, 71-80, 84,90, 105,107
X	EP,A,0 533 350 (MERCK & CO INC) 24 March 1993 see claims; examples ____	1-18,49, 55, 71-80, 84,90, 105,107
X	EP,A,0 547 699 (MERCK & CO INC) 23 June 1993 see claims; examples ____	1-18,49, 55, 71-80, 84,90
X	BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 4, no. 19, 1994 pages 2359-2364, M.D. MULLICAN ET AL. 'The Synthesis and Evaluation of Peptidyl Aspartyl Aldehydes as Inhibitors of ICE' see page 2363, paragraph 2 - paragraph 3; table ____	1-18,49, 55, 71-80, 84,90
P,X	WO,A,95 05192 (MERCK & CO INC ;HAGMANN WILLIAM K (US); MJALLI ADNAN M (US); ZHAO) 23 February 1995 see claims; examples ____	1-18,49, 55, 71-80, 84,90
P,X	EP,A,0 644 197 (STERLING WINTHROP INC) 22 March 1995 see claims; examples ____	1-18
P,X	EP,A,0 644 198 (STERLING WINTHROP INC) 22 March 1995 see claims; examples ____	1-18

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 95/07617

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Please see annex!
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/USA/210

Claims searched completely: 102-109, 111-113, 115-118, 120-124
Claims searched incompletely: 1-101, 110, 114, 119

In view of the large number of compounds falling under claims 1-101, 110, 114,119, and of the absence of any sensible support for these claims in the description, the Search Division considers that it is not economically reasonable to draw a search report covering the intire subject matter of claims 1-101, 110, 114,119. The search for the claims 1-101, 110,114,119 has therefore been limited and includes all the real examples given in the description and covers all similar compounds having the alleged activities as well (see also remark)

Remark: As far as the claim 76 is directed to a method of treatment of the human and/or animal body, the search has been carried out on the alleged effects of the compound and/or composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 95/07617

Patent document cited in search report:	Publication date	Patent family member(s)	Publication date
EP-A-0519748	23-12-92	CA-A- 2071674 JP-A- 5255218 JP-B- 6102642 US-A- 5434248	22-12-92 05-10-93 14-12-94 18-07-95

WO-A-9309135	13-05-93	AU-A- 2885292 CA-A- 2116653 CZ-A- 9401067 EP-A- 0611375 FI-A- 942061 HU-A- 68200 JP-T- 7500828 NO-A- 941629 NZ-A- 244985 PT-A- 101027	07-06-93 13-05-93 15-12-94 24-08-94 04-05-94 29-05-95 26-01-95 04-07-94 27-06-95 28-02-94

WO-A-9314777	05-08-93	AU-B- 3479593	01-09-93

WO-A-9316710	02-09-93	AU-B- 3666893 CA-A- 2129976 EP-A- 0627926 JP-T- 7504194 US-A- 5430128	13-09-93 02-09-93 14-12-94 11-05-95 04-07-95

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EP-A-0533350	24-03-93	CA-A- 2076159 JP-A- 5227961	17-02-93 07-09-93

EP-A-0547699	23-06-93	CA-A- 2085300 JP-A- 5271274 JP-B- 7017676	20-06-93 19-10-93 01-03-95

WO-A-9505192	23-02-95	AU-B- 7714594	14-03-95

EP-A-0644197	22-03-95	AU-B- 6451494 CZ-A- 9401379 FI-A- 942625 JP-A- 7025887	08-12-94 14-06-95 05-12-94 27-01-95

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No

PCT/US 95/07617

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0644197		NO-A- 942065	05-12-94
EP-A-0644198	22-03-95	AU-B- 6347394 CZ-A- 9401355 FI-A- 942624 HU-A- 68689 JP-A- 7089951 NO-A- 942064	27-04-95 15-12-94 04-12-94 28-07-95 04-04-95 05-12-94